IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 9 Ser. 4 (September. 2024), PP 23-34
www.iosrjournals.org

Exploratory Analysis Of Epidemiological, Clinicopathological Characteristics And Prognostic Factors Of Stage IV Epithelial Ovarian Cancers: A Single Institutional Study In Chennai

Dr. Shaoni Parai, Dr B. Ramkumar, Dr. G. Raja, Dr. Manish Kumar Sharma, Dr. Atul J G, Dr. Vasanth Rooban Narasimman

(Medical Oncology/Govt Royapettah Hospital, India)
(Medical Oncology/ Govt Royapettah Hospital, India)
(Medical Oncology/ Govt Royapettah Hospital, India)
(Medical Oncology/ Govt Royapettah Hospital, India)
(Medical Oncology/ Govt Royapettah Hospital, India)
(Medical Oncology/ Govt Royapettah Hospital, India)

Abstract:
Background*: Ovarian cancer (oc) is the 3rd most common cancer (ca) in females in India (globocan 2020)[1], epithelial ovarian cancer consists of 90% of all oc. More than 70% of ovarian ca patients diagnosed at advanced stage due to its asymptomatic nature and insidious onset of the disease. Metastases(mets) remained a major cause of mortality in ovarian cancer patients. This study is being undertaken to identify prognostic and predictive factors associated with the survival of patients with metastatic ovarian cancer.*
Materials and methods*: It is a retrospective study. Patients diagnosed with stage IV epithelial ovarian cancer (treatment naive), who attended the department of medical oncology, Govt Royapettah Hospital (GRH), Chennai during 2013- 2018 with regular follow up included. 5 years follow-up data collected till dec, 2023. Aim of this study is to identify the epidemiological, clinicopathological characteristics, treatment outcome and other prognostic factors predicting overall survival (os) and progression free survival (pfs) in patients with stage IV ovarian cancer.*
Results*: In this study 85 patients with stage IV epithelial ovarian ca were analysed. In our study median os is 27 months, pfs is 13 months. Overall survival (os) rate at 2 years (yr)= 0.5647, overall survival (os) rate at 5 years = 0.105. Progression free survival (pfs) rate at 2 years = 0.1765, progression free survival (pfs) rate at 5 years = 0.0471. Kaplan Meier (KM) survival curves have shown response after 1st line treatment, surgery vs no surgery, platinum sensitive recurrence have significant association with 2 year, 5 year os and pfs ($p<0.05$). Hpe (high grade serous vs less common ovarian cancers) has showed significant correlation with 5 year survival ($p<0.05$), univariate cox regression analysis has shown, number of mets (single site vs multiple site) significantly associated with improved 2 year survival ($p=0.02$) and pfs ($p=0.005$). Both univariate and multivariate analysis showed age (<=56 vs>56) as independent factor correlating with 5 year survival ($p=0.02$), ($p=0.01$), multivariate cox regression analysis showed pretreatment ca 125 is an independent variables for pfs ($p=0.04$).*
Conclusion*: In our study KM survival curves have shown if patients could undergo cytoreductive surgery, had response after 1st line treatment (surgery and chemo) , significant improvement in 2 year, 5 year os and pfs can be achieved, though not established in regression analysis. Recurrence rate remained very high in advanced stage, in our study KM survival curve has shown platinum sensitive recurrence has significantly better 2 year, 5 year os and pfs rate. Cox regression analysis showed patients with single site of mets have significantly better 2 year survival and pfs than patients with multiple site of mets. Pre treatment raised ca 125 found to be an independent factor which can predict poor pfs. Higher age is an independent factor found to impact 5 year os.*
Keywords*: Ovarian cancer, stage IV, cytoreductive surgery, chemotherapy, prognostic factors, overall survival, progression free survival*

Date of Submission: 01-09-2024 Date of Acceptance: 11-09-2024

I. Introduction

Ovarian cancer (OC) is the third most common cancer in females in India as per Globocan 2020 data, while as per incidence rate, including both sexes it is in the ninth rank in India, and globally in eighteenth rank. It is concerning that in India, Ovarian cancer incidence is increasing.[1]

It is typically present in postmenopausal women with the peak incidence occurring in the 60s.[2, 3] However, OC may also be seen in younger women, in which case it is often associated with certain genetic predispositions such as BRCA1 and BRCA2 gene mutations.[4]

Epithelial ovarian cancer (EOC) accounts for 90% of all histological types of OC [3, 5, 6.] and the remaining 10-15% are non-epithelial ovarian carcinomas, such as stromal and germ cell tumors. Five main types of epithelial carcinomas can be distinguished: high-grade (HG) serous (70%), endometrioid (10%), clear cell (10%), mucinous (3%), and low-grade (LG) serous (<5%) [7]

The different EOC subtypes exhibit diverse genetic traits and clinical behavior, with the high-grade serous (HGS) carcinomas being the most aggressive comprising the vast majority of late stage cases.[8]

The majority of ovarian cancer with more than 70% of patients are diagnosed at advanced stage (stage III– IV).[3] OC has been called the "silent killer" because mostly the disease presents as distant disease [9]due to its asymptomatic nature and insidious onset of the disease.

Ovarian cancer can metastasize through the intra peritoneal route, lymphatic channels, and hematogenous route.[10] The most common sites of ovarian cancer spread include peritoneum, liver and lymph nodes.[11-13] Occasionally, distant sites such as bone and brain may be involved.[14-15]

Metastases is a major cause of mortality in ovarian cancer patients,[16] despite the continuous improvement of chemotherapy drugs and advancement of surgical techniques.

Despite the initial response to treatment of advanced OC with chemo, the recurrence rate at these advanced stages of the disease (stages III-IV) may be as high as 80%, usually because of chemotherapy resistance.[5]

In 2013, FIGO revised the staging system with subgrouping of stage IV cases into stage IVA and IVB [17]. Thus, the current FIGO stage IVA includes cytologically proven pleural effusion, whereas stage IVB encompass all other stage IV cases (distant organ and non-regional nodal metastases).

In spite of significant mortality in metastatic setting, very few patients have been found with long term survival. But predictive factors are not exactly known.

Identification of prognostic and predictive factors is essential to improve the survival. To the best of our knowledge, there is lack of these types of studies from our region, so this study is undertaken to comprehend real word scenario in a resource limited setting.

II. Materials And Methods:

This retrospective study done in patients diagnosed with stage IV ovarian cancer (treatment naive), who attended the Department of Medical Oncology, GRH, Chennai during Jan 2013- Dec 2018 with regular follow up.

Study design: It is a retrospective study.

Study location: This is a single Centre study done in the department of medical oncology, Govt Royapettah Hospital, Chennai

Study duration: Jan 2013- Dec 2018 and follow up data collected till Dec 2023.

Study sample: It is an exploratory study, so all patients with data details, presented with stage IV ovarian cancer who attended the department of medical oncology Jan 2013- Dec 2018 was taken.

Subjects and selection methos:
Inclusion criteria:
Patients diagnosed with stage IV epithelial ovarian cancer.

Exclusion criteria:
1. Patients who lost data or lost follow up were excluded.
2. Patients with multiple malignancies were excluded.

Procedure methodology:

Database retrieved from medical records of patients who attended the Department of Medical Oncology, GRH, Chennai during 2013- 2018 and were diagnosed with stage IV epithelial ovarian cancer

(treatment naive), who underwent treatment in the hospital and on completion of treatment, did regular follow-up. 5 year follow-up data for study was collected till Dec, 2023.
Staging was based on the AJCC/FIGO staging system.

Database including demographics, age, parity, menopausal status, body mass index (BMI), serum cancer antigen (CA)-125 levels and other tumor markers, coexisting morbidity, vital status, presence of ascites, histopathological(HPE) subtype, tumor characteristics, staging, nodal and other visceral metastasis, type of primary treatment, surgical debulking status, and follow-up information were collected. Overall Survival (OS) and Progression free survival (PFS) had been calculated from records.

The epidemiological, clinicopathological characteristics, treatment outcomes and other prognostic factors predicting overall survival (OS) and progression free survival (PFS) are analysed.

PFS determined by calculating the interval from the time of start of primary treatment to the first evidence of recurrence, progression of disease, death, or last follow-up, whichever occurred first.

OS defined as the interval from the time of start of primary treatment until death from all causes or last follow-up since completion of treatment for patients who are still alive, whichever occurred first.

Objectives And End Points:

Our objective is to study the epidemiological, clinicopathological characteristics, treatment outcome and other prognostic factors predicting overall survival (OS) and progression free survival (PFS) in patients with stage IV ovarian cancer.

Our primary endpoint is overall survival and factors predicting overall survival in stage IV ovarian cancer, with association between those factors and overall survival.
And secondary end point is progression free survival and factors predicting PFS.

Statistical Analysis:

Data analysis performed using R software and descriptive statistics computed for all patients' baseline characteristics. Characteristics of patients described using mean and standard deviation (if normally distributed) or median and interquartile range (if skewed) for continuous variables and by frequencies and percentages for categorical variables. Kaplan-Meier estimated PFS and OS, time stratified by the various predictive factor categories calculated and compared by employing the log-rank test statistics. Multivariate Cox proportional hazard models used to assess the association between participants' clinicopathologic characteristics and survival outcomes while adjusting for other covariates.
Associations regarded as significant if $P < .05$. All P values are two-sided.

III. Results

Clinical Characteristics and Epidemiology:

In our study data collected from 85 patients with Stage IV epithelial Ovarian Ca. Most commonly patients presented in 5th Decade, lowest age 35 year, highest-75year, median age 56.

At presentation, 76(89.4%) patients were postmenopausal**,** only 9**(**10.5%) were premenopausal. Noting parity history 5.8 %(n=5) had history of nulliparity,8.2%(n=7) had uniparity,85.8%(n=73) had multiparity.

Most commonly patients (84.7%) presented with complaints of abdominal distension or pain, followed by other symptoms were loss of appetite, shortness of breath, low back pain.

Only two patients had given positive family history of cancer. 35.2 % of patients had existing comorbidity.

At presentation, most commonly patients were having ECOG PS 1- 52.9%(n=45), followed by PS2-43.5%(n=37) and PS 3-3.5%(n=3). Median BMI found in our study population was 25.2, two patients found to be underweight <18.5, five patients found to have obesity (>=30).

Ascites was seen in most of the patients- 61.1% (52), among them mild ascites found in 9 patients, moderate ascites in 30 patients, and massive ascites in 13 patients. No ascites was seen in 38.8% patients (33).

Histopathology

Among our study subsets, most commonly patients were diagnosed to have histology with High grade serous carcinoma-65(76.4%), followed by undifferentiated-7(8.2%), clear cell-5(5.8%), mucinous-4(4.7%), low grade serous-2(2.3%) and endometrioid-2 (2.3%).

Tumor Marker

Highest value of pretreatment CA 125 was found to be 40,000 while lowest was 4, median ca 125 found to be-664.Other than CA 125, serum CEA was found to be raised in 3 patients with median value-67.

Staging And Metastatic Sites

In our study with stage IV ovarian cancer, mostly patients presented in stage IVB-63.5% (n=54), presented in stage IVA are 36.4%(n=31).

Mostly patients presented with metastases in single site -78.8%(n=67) and multiple sites are-21.1%(n=18)

Site specific metastases found were metastases in single site, pleural effusion-31(36.4%), liver-14 (16.4%), non-regional lymph nodal (Non reg LN)-14 (16.4%), lung-14(16.4%).

Multiple sites of metastases found in pleura with other sites -6(7%), liver and other sites-12 (14.1%), bone-4(4.7%), abdominal wall-4(4.7%), brain-2(2.3%)

Treatment Details

In our study total 56 (65.8%) patients underwent primary cytoreduction (PCR) or interval cytoreduction (ICR). 29 (34.1%) patients did not undergo any surgery.

Patients who underwent surgery, only 6(7%) patients could undergo primary cytoreduction. Patients underwent interval cytoreduction, after receiving neoadjuvant chemo (NAC) were-50 (58.8%). Those who underwent surgery 39.2 % patients had achieved R0 resection.

No patient in our setting had received intra peritoneal therapy.

Most of the patients (82.3%) (n=70) had received Paclitaxel (Pacli) and Carboplatin (carbo) as 1st line chemo.

In view of poor general condition, chemo could not be given in two patients and managed with best supportive care.

Response assessment done with history, physical examination and tumor markers, imaging (as indicated).

With primary treatment (surgery and 1st line chemo), 42.3 %(n=36) patients achieved complete response (CR).43.5% (n=37) patients achieved partial response (PR), while 14.1% (n=12) patients progressed (PD).

Recurrence:

In our study though patients achieved good response with 1st line treatment, but 94.1 % patients showed recurrence till the last date of follow up. Further classifying as per Platinum sensitivity- Platinum sensitive recurrence was 54.1%(n=46), Platinum resistant recurrence was 29.2%(n=24), Platinum refractory was11.7% (n=10).

Most commonly patients recurred locally (38.75%), followed by liver (16.25%), lung (16.25%), lymph nodal (8.7%).

Patients with platinum sensitive recurrence mostly received doublet chemo- platinum agents along with Taxane/Gemcitabine/cyclophosphamide/liposomal doxorubicin as 2nd line chemo, while patients with platinum resistance mostly received liposomal doxorubicin-based chemo regimens.

In view of resources limited setting only 10.5 % patients received Bevacizumab along with chemo in adjuvant and maintenance setting.

Only 6 patients were assessed for BRCA1 and 2 testing, among them one patient with recurrence post multiple lines of chemo were started on Olaparib, but patient did not tolerate, developed uncontrollable fatigue and had to discontinue.

Currently 28.7% are receiving 3rd line chemo, and 17.5% are on 4th line. While three (3.5%) patients are receiving 8th line chemo.

Four patients received palliative RT. Two patients received Whole Brain RT (WBRT), two patients received palliative RT for skeletal mets.

Table 1: Frequency Of Clinical Characteristics

Clinical Characteristics	No	Percentage
Menstrual History		
Postmenopausal	76	89.4
Premenopausal	9	10.5
Histopathology		
High Grade Serous Ca	65	76.4
Undifferentiated	7	8.2
Clear Cell	5	5.8
Mucinous	4	4.7
Low Grade Serous	2	2.3
Endometrioid	2	2.3
Ascites	52	61.1
Mild	9	17.3
Moderate	30	57.6
Massive	13	25
Ecog Ps		

Ps1	45	52.9
Ps2	37	43.5
Ps3	3	3.5
Presenting Stage		
Stage IVA	31	36.4
Stage IVB	54	63.5
Mets Site Number		
Single Site	67	78.8
Multiple Site	18	21.1
Mets Site		
Plural Effusion	31	36.4
Plura With Other Sites	6	7
Liver Only	14	16.4
Liver With Other Sites	12	14.1
Non Reg LN Only	14	16.4
Non Reg LN With Other Sites	4	4.7
Lung Only	4	4.7
Lung With Other Sites	10	11.7
Abd Wall (Single/ With Other Sites)	4	4.7
Bone (With Other Sites)	4	4.7
Brain (With Other Sites)	2	2.3
Surgery		
PCR	6	7
ICR	50	58.8
No Surgery	29	34.1
Pacli, Carbo As 1st Line Chemo	70	82.3
Response To Primary Treatment (Surgery+Chemo)		
CR	36	42.3
PR	37	43.5
PD	12	14.1
Recurrence		
Platinum Sensitive	46	54.1
Platinum Resistant	24	29.2
Platinum Refractory	10	11.7

Table No 1 is tabulated form of above mentioned text.

Complications:

Surgical: Immediate post op complications most commonly seen were infection, haemorrhage, wound complications. In immediate post op duration, no patient died. Most common delayed complication found was bowel adhesion.

Chemotherapy Related: Most common complications found to have myelosuppression followed by gastro intestinal toxicity followed by peripheral neuropathy. Most common grade 3 side effect was neutropenia. Among peripheral neuropathy grade 1found in 57.6% patients, grade 3 neuropathy seen in 8.2 %.

9.41% Patients developed allergic drug reaction with taxane and 3.5 % developed allergic reaction with Carboplatin. Managed with anti-histamines. Grade 3 allergic drug reactions seen only in 2.3%, managed systemically.

Survival Analysis

In our study in overall cohort at 5 years median OS is 27 months, PFS is 13 months, while highest OS is 10 years, achieved by two patients.

Median OS for stage IV A patients is 36 months, median PFS is 19 months, for stage IV B patients median OS is 24 months, PFS is 12 months. For patients with only non regional LN mets- median OS is 55 months, PFS is 23 months.

Overall Survival (OS) rate at 2 years = 0.5647, Overall Survival (OS) rate at 5 years = 0.105.

Progression Free Survival (PFS) rate at 2 years = 0.1765, Progression Free Survival (PFS) rate at 5 years = 0.0471.

KM survival curves showed survival at 2 yrs,5 yrs significantly improved.

1.If patients achieved CR with 1st line treatment>PR>PD ($p < 0.0001$).

2. If cytoreduction surgery could be done, though no difference found between PCR or ICR vs no surgery ($p < 0.0001$).

3.Patients had Platinum sensitive recurrence>resistant>refractory ($p < 0.0001$).

Survival at 2 yrs significantly improved with single site of mets vs multiple site of mets ($p=0.017$), at 5 years though significantly improved but could not achieve statistical significance($p=0.054$).

HPE (High grade serous vs less common ovarian ca) showed significant correlation with 5 year survival(p=0.007), while failed to show any significance at 2 years (p=0.062).

Though patients' median OS and PFS is better in non regional lymph nodal mets>pleural mets>other distant mets.

No statistical correlation from KM curves could be established in our study with 2 yrs /5 yrs survival and variables like staging (IV A vs IV B), presence of ascites, menopausal status, pre treatment CA 125 level, site of mets.

Patients who did not recur had significantly better 2 yr, 5 yr OS.

KM curves showed significant improvement in PFS with

1.Response after 1st line treatment(p<0.0001)
2.Surgical status(p<0.0001)
3.Platinum sensitive recurrence(p<0.0001)
4.No of site of mets (single vs multiple) (p=0.006)
5.pretreatment CA 125(p=0.047)

While no correlation found from KM curves with PFS and variables like staging (IV A vs IV B), presence of ascites, menopausal status, site of mets, histopathology found.

Kaplan-Meier Survival Curves

Figure 1. Response after first line management
A: Survival at 5 years
B: Survival at 2 years

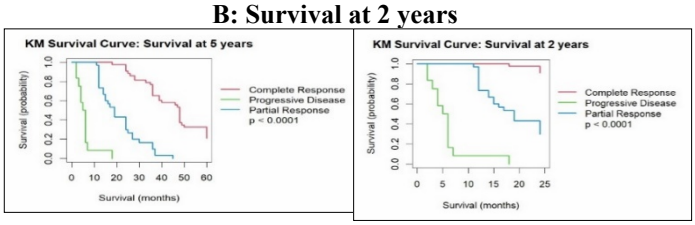


Figure 2. Staging –IVA or IVB
A: Survival at 5 years
B: Survival at 2 years

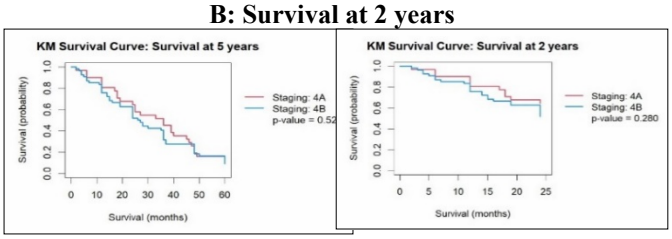


Figure 3. Ascites
A: Survival at 5 years
B: Survival at 2 years

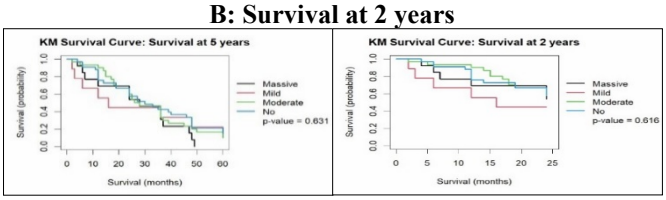


Figure 4. Surgical Status
A: Survival at 5 years
B: Survival at 2 years

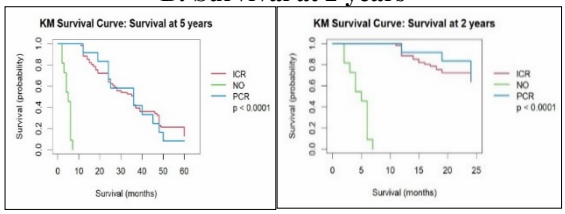


Figure 5. Primary Treatment
A: Survival at 5 years
B: Survival at 2 years

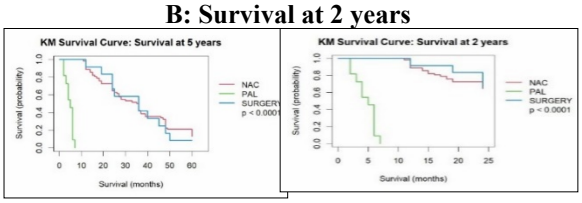


Figure 6. Platinum Sensitivity
A: Survival at 5 years
B: Survival at 2 years

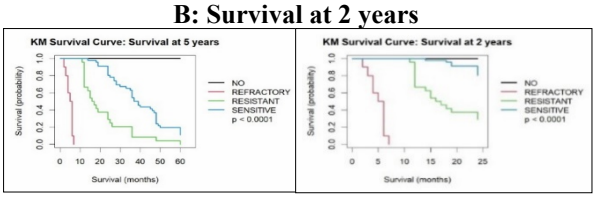


Figure 7. No. of site of mets
A: Survival at 5 years
B: Survival at 2 years

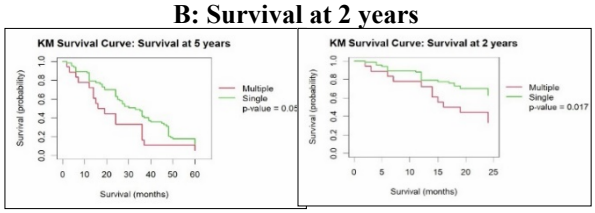


Figure 8. Menopausal Status
A: Survival at 5 years
B: Survival at 2 years

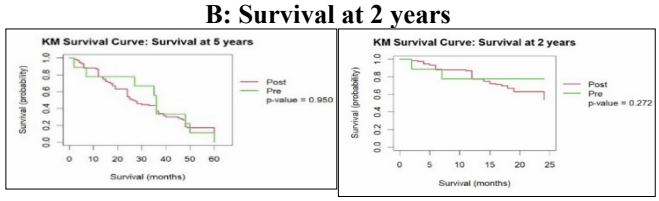


Figure 9. CA-125 level
A: Survival at 5 years
B: Survival at 2 years

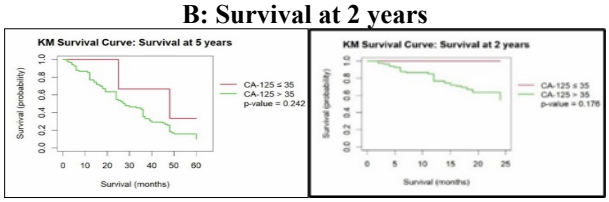
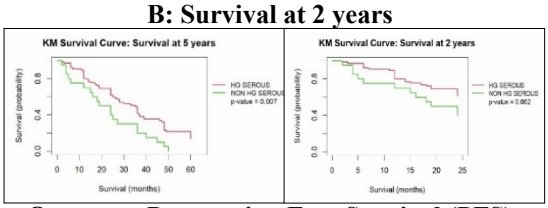


Figure10. Histopathology (HG Serous vs less common ovarian cancers)
A: Survival at 5 years
B: Survival at 2 years



Outcome: Progression Free Survival (PFS)

Figure 11. Response after first line treatment

Figure 12. Staging – 4A or 4B

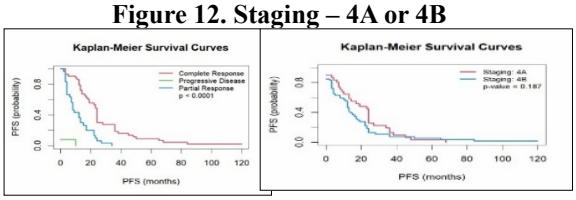


Figure 13. Ascites

Figure 14. Surgical Status

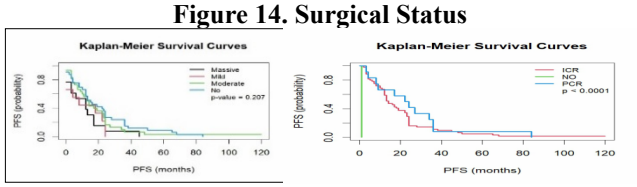


Figure 15. Primary Treatment

Figure 16. Platinum Sensitivity

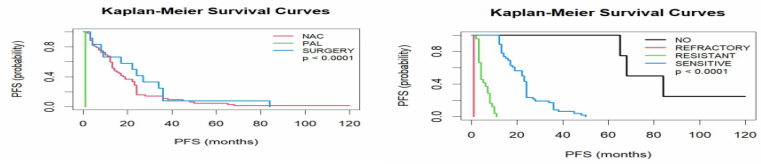


Figure 17. No. of mets

Figure 18. Menopausal status

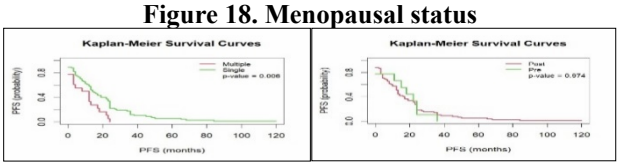


Figure 19.CA-125 level

Figure 20. Histopathology(HG Serous vs less common ovarian)

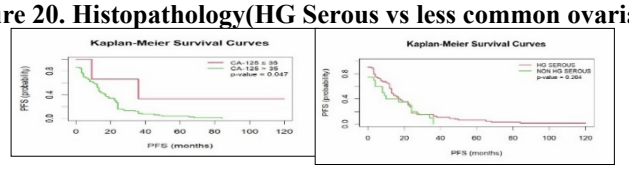


Table 2. Univariate And Multivariate Cox Regression Analysis

Survival At 2 Years

Survival At 2 Years			
Variable	Univariate Analysis	Multivariate Analysis	
	P-Value	HR (95% Ci)	P-Value
Age			
≤56	0.127	Ref	0.307
>56		1.439 (0.716-2.894)	
Staging			
IVA	0.282	Ref	0.608
IVB		1.233 (0.554-2.743)	
Ascites			
No + Mild	0.647	Ref	0.44
Moderate + Massive		0.773 (0.401-1.487)	
Surgical Status			
No	0.997		
ICR + PCR			
Primary Treatment			

Pal	0.995		
NAC + Surgery			
No. Of Mets			
Single	**0.021**	Ref	0.058
Multiple		2.154 (0.975-4.758)	
Menopausal Status			
Pre	0.279	Ref	0.274
Post		2.333 (0.511-10.655)	
Ca-125 Level			
≤35	0.996		
>35			

Survival At 5 Years

Survival At 5 Years			
Variable	Univariate Analysis	Multivariate Analysis	
	P-Value	HR (95% Ci)	P-Value
Age			
≤56	**0.022**	Ref	**0.013**
>56		1.820 (1.137-2.913)	
Staging			
IVA	0.49	Ref	0.45
IVB		1.226 (0.723-2.080)	
Ascites			
No + Mild	0.447	Ref	0.545
Moderate + Massive		1.152 (0.728-1.825)	
Surgical Status			
No	0.995		
ICR + PCR			
Primary Treatment			
Pal	0.995		
NAC+ Surgery			
No. Of Mets			
Single	0.057	Ref	0.169
Multiple		1.528 (0.835-2.794)	
Menopausal Status			
Pre	0.916		
Post			
Ca-125 Level			
≤35	0.268	Ref	0.244
>35		2.330 (0.561-9.666)	

Table 3. Univariate And Multivariate Cox Regression Analysis: PFS

Progression Free Survival			
Variable	Univariate Analysis	Multivariate Analysis	
	P-Value	HR (95% Ci)	P-Value
Age			
≤56	0.186	Ref	0.147
>56		1.388 (0.892-2.159)	
Staging			
4a	0.198	Ref	0.209
4b		1.385 (0.833-2.303)	
Ascites			
No + Mild	0.405	Ref	0.258
Moderate + Massive		1.292 (0.828-2.016)	
Surgical Status			
No	0.995		
ICR + PCR			
Primary Treatment			
Pal	0.995		
NAC + Surgery			
No. Of Mets			
Single	**0.005**	Ref	0.062
Multiple		1.767 (0.971-3.215)	
Menopausal Status			
Pre	0.911		
Post			
Ca-125 Level			
≤35	0.069	Ref	**0.048**
>35		4.327 (1.010-18.545)	

Table 2 A, B, 3 shows

Univariate cox regression analysis showed single site vs multiple sites of mets significantly correlated with 2 year survival (p=0.021) and PFS(p=0.005).

Multivariate cox regression analysis showed pretreatment CA 125 is an independent correlating factor correlating with PFS(p=0.048).

While both univariate and multivariate analysis showed age (<=56 vs >=56) is an independent factor related with 5 year OS.

IV. Discusssion

We collected data of 85 patients with upfront, treatment naive stage IV epithelial ovarian cancer and analysed further. Pretreatment factors we evaluated were age, parity, menopausal status, BMI, serum cancer antigen (CA)-125 levels, coexisting morbidity, presence of ascites, ECOG performance status. In our study Uni and multivariate analysis showed age (<=56 vs>56) is an independent factor associated with 5 year survival, this correlating with multiple studies like Steinberga I et al[7], Okunade et al[3], Wang Y et al[24], Deng et al[11] where age found to be a significant prognostic factor for survival. This may be because age related impact on patient ability to cope with stress related to a chronic disease state, and the altered physiology of the elderly alters the pharmacokinetics and pharmacodynamics of upfront chemotherapeutic agents used in the treatment of ovarian cancer.[3]

But in our study BMI, parity history, menopausal status, presence of ascites have not shown any significant association, in contrast to Okunade et al study[3] where being premenopausal was an independent predictor of reduced OS and Kim et al[25] study which reported a previous parous event was associated with decreased mortality risk compared to nulliparity. On the contrary Trifanescu et al [26] showed premenopausal patients with OC had a better long-term outcome and also showed increased BMI is a predictor of worst

prognosis in patients with ovarian cancer. Hamilton CA et al showed that lower CA-125 value, absence of ascites, stage at presentation had significant influence on long term survival.[27]

Though in our study patients performed worse with multiple co morbidities and with poor PS, but did not show any statistical significance.

In our study most of the patient population consisted of post menopausal and old aged, suggestive of higher prevalence of advanced disease status in this group of population.

During evaluation in our study mostly patients presented with high grade serous histology like other literature Ehman S [28], Steinberg I [7], Deng et al [11]showed. In our study HPE (High grade serous vs less common ovarian cancers) showed significant correlation with 5year survival(p=0.007), while failed to show any significance with 2 years OS and PFS. Deng K, Yang C et al [11] showed serous cell-type tumors had better prognosis. HPE could not show any consistent co relation in advanced setting.

Both uni and multivariate analysis showed ca 125 (<=35 vs >35) value is an independent factor associated with improved PFS in our study, like Schneider D et al study [23]. Wang Y et al [24] study has shown the risk of 2-year overall mortality is higher in patients with raised CA125.

Studies reported that CA125 level is increased in 80% of the patients with epithelial ovarian cancer and 90% with epithelial ovarian cancer at advanced stage [29]

In our study patients mostly presented in stage IVB-63.5%, patients presented in in stage IVA are 36.4%. Mostly (78.8%) patients presented with single site metastases and multiple sites are-21.1%.

Site specific metastases found were, pleural effusion-36.4%, liver alone-16.4%, liver and other sites-14.1%, non regional lymph nodal only-16.4%, lung-16.4%, like Deng et al study where most common distant metastatic sites are liver, distant lymph nodes, and lung.[11]

In our study Univariate Cox regression analysis has shown- number of metastatic sites (single site vs multiple sites) significantly associated with improved 2 year OS, Both uni and multivariate analysis showed number of mets is an independent prognostic factor for PFS, consistent with Deng et al study which showed patients with multiple distant metastatic sites had significantly shorter overall survival than patients with only one site of distant metastases [11]

In our study median OS for stage IV A patients is 36 months, median PFS is 19 months, for stage IV B patients median OS is 24 months, PFS is 12 months, for patients with only non regional LN mets- median OS is 55 months, PFS is 23 months. Median OS and PFS is better in non regional lymphnodal mets compared to stage IV A and other distant organ mets.

Though in our study median PFS and OS is better in stage IV A vs IV B, but it failed to achieve any statistical significance.

Hjerpe et al [30]showed Median OS for women with LN was 41.4 months, compared to 25.2 and 26.8 months for patients with pleural or other/multiple distant metastases .

Deng K et al [11]showed overall survival significantly higher for distant lymph node metastases compared to pleural and visceral mets. Steinberga I et al[7,] Hjerpe E at al study[25]showed site of stage IV metastatic disease to be associated with survival. Lymph node only mets showed longer survival in their study. Their results suggest that disease disseminating predominately through the lymphatics would have a less aggressive nature than that directly invading the pleura or spreading hematogenously.[25]

In our study 65.8% patients underwent cytoreductive surgery. In view of metastatic setting mostly (58.8%) patients underwent interval cytoreduction after receiving neoadjuvant chemo.34.1% patients could not undergo any surgery in view of low resectability or any reason for in operability. Those who undergo surgery 39.2 % of them, have achieved R0 resection.

In our study Kaplan Meier survival curve has shown surgery vs no surgery, have significant association with 2yr, 5 yr OS and PFS (p<0.05). Similar to our study, Sarwar A H et al[18], Dabi Y et al [19]showed patients treated solely with chemotherapy without surgery had a signifcantly worse PFS and OS than patients that underwent PDS or NACT–IDS. Dabi Y et al showed better survival when complete surgery is achieved, despite a distant metastasis, showing similarity with Winter et al study.[20]

Most of the patients (82.3%) in our study had received 3 weekly Paclitaxel(175 mg/m2) and Carboplatin(AUC 5) as per EORTC 55971[31],CHORUS trial [32] . With primary treatment (surgery and 1st line chemo), in our study 42.3 % patients achieved complete response (CR). KM Survival curve has shown response after 1st line treatment has significant association with 2 yr, 5 yr OS and PFS, which is comparable with Sarwar et al study which showed response to initial chemotherapy, complete remission after induction therapy are significant prognostic factors for long term survival.

The use of a combined platinum and taxane based chemotherapy regimen had an independent positive impact on overall survival in Dabi Y et al [19], Atavensen et al study [33]. The importance of the chemotherapy is enhanced by the presence of extra–abdominal disease that cannot be cured otherwise.

Dabi Y [19], Deng K [11], Steinberga I et al[7,] Hjerpe E at al study[25] showed, cytoreductive surgery, platinum combination chemotherapy were good prognostic factors. Neoadjuvant chemotherapy followed by delayed

cytoreductive surgery may prevent unnecessary postoperative morbidity and mortality [34,35] and promote higher chances of achieving complete cytoreduction during surgery.[36]

Our study did not find any difference in OS or PFS between PCR vs NAC and ICR group, like Griffith et al [21], Cheasley et al [22], Steinberga I et al study[7] which also showed no significant diference in survival between stage IV patients received NACT + IDS(Interval debulking surgery) or PDS(Primary debulking surgery).

In our study in overall cohort at 5 years median OS is 27 months, PFS is 13 months, while highest OS is 10 years, achieved by two patients, one had HG serous ca, with stage IV A presentation, underwent ICR. One patient had LG serous ca with non regional LN mets, underwent PCR. Both patients have received Paclitaxel, Carboplatin as neo adjuvant and adjuvant chemo.

Overall Survival (OS) rate at 2 years = 0.5647, Overall Survival (OS) rate at 5 years = 0.105. like Wang Y et al study where 2 year OS is 52.5%, Steinberg et al study had shown 5-year overall survival rate in stage IV is 9%.

Progression Free Survival (PFS) rate at 2 years = 0.1765, Progression Free Survival (PFS) rate at 5 years = 0.0471.

In our study 94.1 % patients showed recurrence till the last date of follow up with platinum sensitive recurrence seen in 54.1% of patients, KM Survival curve has shown patients who did not recur had significant improved 2 yr, 5 yr OS. Recurrence with platinum sensitivity, have significant association with 2 yr, 5 yr OS and PFS.

Sarwar et al [18]had shown in their study significant number of patients achieve complete biochemical and radiological response with advanced treatment modalities, however patients with stage IV disease tend to relapse within eighteen months after treatment completion [37]. Among the relapsed patients, in whom tumor remains sensitive to platinum-based chemotherapy, outcomes are good as compared to those whose disease becomes platinum refractory in subsequent relapses [37].

Currently 28.7% are receiving 3rd line chemo, and 17.5% are on 4th line. While three patients are receiving 8th line chemo.

Ehman S et al[28] showed in their study 18.3% received 3 lines, 9.8% received 4 lines,5.9% received 7 lines, 2.0%received 8 lines, 0.7% received 9 lines. Hanker et al[38] found that patients receiving third and fourth lines of chemotherapy have a 3.5-month PFS gain compared to patients not undergoing treatment. The study also reported an impact on OS for third-, fourth-, and fifth-line treatment. They concluded that 3 lines of chemotherapy in the recurrent setting are beneficial, but additional lines may not be helpful [38]. In the recurrent setting, platinum-based chemotherapy is favorable to treat patients with ovarian cancer and is used in different combinations until platinum-resistance develops[39].

Similar to these studies in our setting patients with platinum sensitive recurrence mostly received platinum based doublet chemo, while patients with platinum resistance mostly received liposomal doxorubicin-based chemo regimens.

In view of resources limited setting only 10.5 % patients received Bevacizumab along with chemo in adjuvant and maintenance setting as per GOG-0218 and ICON 7 trial [40,41], though any statistical significance not achieved. Only one patient with germline BRCA 1 mutation, with recurrence post multiple lines of chemo was started on Olaparib [42], but patient did not tolerate and stopped pre-maturely.

LIMITATION: Our study is a retrospective, single institutional study, done on small sample size. In view of resources limited setting genetic testing could not be done in optimal sample. Bevacizumab, PARP inhibitors could not be utilized optimally in indicated population.

V. Conclusion

In our study at 5 years median OS is 27 months, PFS is 13 months. Overall Survival (OS) rate at 2 years = 0.5647, Overall Survival (OS) rate at 5 years = 0.105. Progression Free Survival (PFS) rate at 2 years = 0.1765, Progression Free Survival (PFS) rate at 5 years = 0.0471.

Median OS and PFS is better in nonregional lymphnodal mets>malignant pleural effusion>other distant/visceral/multiple mets, though not achieved any statistical significance,

KM Survival curves have shown if patients could undergo cytoreductive surgery, achieved response after 1st line treatment (surgery and chemo) have very significant improvement in 2 yr, 5 yr OS and PFS, though not established in regression analysis. In spite of achieving good response with primary management, recurrence rate remained very high in advanced stage, in our study KM survival curve has shown platinum sensitive recurrence has significantly better 2 yr, 5 yr OS and PFS rate. Cox regression analysis showed patients with single site of mets have significantly better 2 year survival and PFS than patients with multiple sites of mets. Pretreatment raised CA 125 found to be an independent factor which can predict poor PFS. Higher age is an independent factor found to impact 5-year OS.

Declaration: The study was conducted in the hospital with no extra funds from patients, after ethical approval from the internal ethics committee. There are no conflicts of interest.

VI. References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: Cancer J Clin. (2021) 71(3):209–49.
2.Okunade KS, Adejimi AA, Ohazurike EO, et al:Predictors of Survival Outcomes After Primary Treatment of Epithelial Ovarian Cancer in Lagos, Nigeria. JCO Glob Oncol. 2021 Jan;7: 89-98.
3. Okunade KS, Okunola H, Okunowo AA, et al: A five-year review of ovarian cancer at a tertiary institution in Lagos, South-West, Nigeria. Niger J Gen Pract 14:23-27, 2016.
4. Matulonis UA, Sood AK, Fallowfield L, et al: Ovarian cancer. Nat Rev Dis Primers 2:16061, 2016
5. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2020. CA Cancer J Clin 70:7-30, 2020
6. Bray F, Ferlay J, Soerjomataram I, et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394-424, 2018
7. Steinberga I, Jansson K, Sorbe B. Quality Indicators and Survival Outcome in Stage IIIB-IVB Epithelial Ovarian Cancer Treated at a Single Institution. In Vivo. 2019 Sep-Oct;33(5):1521-1530..
8. Kobel M, Kalloger SE, Huntsman DG, et al. Differences in tumor type in low-stage versus high-stage ovarian carcinomas. Int J Gynecol Pathol. 2010; 29:203–211.
9. M.D. Danijela Jelovac, D.K. Armstrong, Recent progress in the diagnosis and treatment of ovarian cancer, CA Cancer J. Clin. 61 (2011) 183–203
10. P.G. Rose, M.S. Piver, Y. Tsukada, T.S. Lau, Metastatic patterns in histologic variants of ovarian cancer. An autopsy study, Cancer 64 (1989) 1508–1513.
11. K. Deng, et al., Sites of distant metastases and overall survival in ovarian cancer: A study of 1481 patients, Gynecol Oncol(2018).
12. S.A. Cannistra, Cancer of the ovary, N. Engl. J. Med. 351 (2004) 2519–2529.
13. U. Guth, D.J. Huang, G. Bauer, M. Stieger, E. Wight, G. Singer, Metastatic patterns at autopsy in patients with ovarian carcinoma, Cancer 110 (2007) 1272–1280.
14. J. Sehouli, J. Olschewski, V. Schotters, C. Fotopoulou, K. Pietzner, Prognostic role of early versus late onset of bone metastasis in patients with carcinoma of the ovary, peritoneum and fallopian tube, Annals of Oncology: Official Journal of the
European Society for Medical Oncology 24 (2013) 3024–3028.
15. C.Marchetti, G. Ferrandina, G. Cormio, A. Gambino, S. Cecere, D. Lorusso, et al., Brain metastases in patients with EOC: Clinico-pathological and prognostic factors. A multicentric retrospective analysis from the MITO group (MITO 19), Gynecol.
Oncol. 143 (2016) 532–538.
16. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: Cancer J Clin. (2018) 68(1):7–30.
17.Prat J. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet. 2014; 124:1–5**.**
18.Sarwar A H et al. Factors Favoring Long Term Survival in Patients with Stage IV Epithelial Ovarian Cancer: An Institutional Research. Asian Pac J Cancer Care, 5 (1), 15-18.
19.Dabi Y et al. Patients with stage IV epithelial ovarian cancer: understanding the determinants of survival. J Transl Med (2020) 18:134
20.William E. Winter III et al. Prognostic Factors for Stage III Epithelial Ovarian Cancer: A Gynecologic Oncology Group Study. J Clin Oncol 25:3621-3627. © 2007 by American Society of Clinical Oncology
21.Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. Natl Cancer Inst Monogr1975; 42:101–4.
22. Cheasley D, Wakefield MJ, Ryland GL, Allan PE, Alsop K, Amarasinghe KC, et al. The molecular origin and taxonomy of mucinous ovarian carcinoma. Nat Commun2019; 10:3935.
23.Schneider D, Halperin R, Halperin D, et al: Prediction of the survival of patients with advanced ovarian cancer according to a risk model based on a scoring system. Eur J Gynaecol Oncol 19:547-552, 1998.26
24. Wang y et al. Prediction for 2-year mortality of metastatic ovarian cancer patients based on surveillance, epidemiology, and end results database.15 September 2022.10. 3389.fsurg.2022.974536.
Cornelis S, Van Calster B, Amant F, et al. Role of neoadjuvant chemotherapy in the management of stage IIIC-IV ovarian cancer: survey results from the members of the European Society of. Int J Gynecol Cancer. 2012; 22:407–416.
25. Kim SJ, Rosen B, Fan I, et al: Epidemiologic factors that predict long-term survival following a diagnosis of epithelial ovarian cancer. Br J Cancer 116:964-971, 2017
26. Trifanescu OG, Gales LN, Trifanescu RA, et al: Clinical prognostic factors in pre- and post-menopausal women with ovarian carcinoma. Acta Endocrinol (Buchar) 14:353-359, 2018

27. Hamilton CA, Miller A, Casablanca Y, Horowitz NS, Rungruang B, Krivak TC, Richard SD, Rodriguez N, Birrer MJ, Backes FJ, Geller MA. Clinicopathologic characteristics associated with long-term survival in advanced epithelial ovarian cancer: an NRG Oncology/Gynecologic Oncology Group ancillary data study. Gynecologic oncology. 2018;148(2):275-80
28. Ehmann S, Shay K, Zhou Q, Iasonos A, Sonoda Y, Gardner GJ, Long Roche K, Zammarrelli WA 3rd, Yeoushoua E, O'Cearbhaill RE, Zivanovic O, Chi DS. Outcomes and long-term follow-up by treatment type for patients with advanced-stage ovarian cancer managed at a tertiary cancer center: A Memorial Sloan Kettering Cancer Center Team Ovary study. Gynecol Oncol. 2023 Feb; 169:118-124. doi: 10.1016/j.ygyno.2022.12.009.
29.Asali A, Haj-Yehia N, Zehavi T, Perry T, Beiner M, Fishman A, et al. High grade, advanced, serous ovarian cancer with low serum CA125 levels. J Obstet Gynaecol. (2021) 41(7):1107–11. doi: 10.1080/01443615.2020.1835844
30.ElisabetHjerpe, Christian Staf, Pernilla Dahm-Kähler,et al(2018) Lymph node metastases as only qualifier for stage IV serous ovarian cancer confers longer survival than other sites of distant disease – a Swedish Gynecologic Cancer Group (SweGCG) study , Acta Oncologica, 57:3, 331-337
31. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010; 363:943-953.
32. Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet 2015; 386:249-257. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26002111.
33. Ataseven B, Grimm C, Harter P, Heitz F, Traut A, Prader S, et al. Prognostic impact of debulking surgery and residual tumor in patients with epithelial ovarian cancer FIGO stage IV. Gynecol Oncol. 2016;140(2):215–20
34. Vergote I, Amant F, Kristensen G, Ehlen T, Reed NS and Casado A: Primary surgery or neoadjuvant chemotherapy followed by interval debulking surgery in advanced ovarian cancer. Eur J Cancer 47(3): S88-92, 2011. PMID: 21944035. DOI: 10.1016/ S0959-8049(11)70152-6.
35.Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, Luesley D, Perren T, Bannoo S, Mascarenhas M, Dobbs S, Essapen S, Twigg J, Herod J, McCluggage G, Parmar M and Swart AM: Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an openlabel, randomised, controlled, non-inferiority trial. Lancet 386(9990): 249-257, 2015. PMID: 26002111. DOI: 10.1016/ S0140-6736(14)62223-6
36. Eggink FA, Koopmans CM and Nijman HW: Surgery for patients with newly diagnosed advanced ovarian cancer: which patient, when and extent? Curr Opin Oncol 29(5): 351-358, 2017. PMID: 28614136.
37. Jayson GC, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. The Lancet. 2014;384(9951):1376-88.
38. Hanker LC, Loibl S, Burchardi N, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol. Oct 2012;23(10):2605–2612. doi:10.1093/annonc/mds203.
39. Luvero D, Milani A, Ledermann JA. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. Ther Adv Med Oncol. Sep 2014;6(5):229–39. doi:10.1177/1758834014544121.
40. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011; 365:2473-2483.
41. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011; 365:2484-2496.
42.Kim G, Ison G, McKee AE, et al. FDA approval summary: olaparib monotherapy in patients with deleterious germline BRCA-mutated advanced ovarian cancer treated with three or more lines of chemotherapy. Clin Cancer Res 2015; 21:4257-4261.

VII. Acknowledgment

My sincere thanks to my respected teachers, my colleagues, DR J Kannan Sir (Preceding Chief of the Medical Oncology Departemnt, GRH), to my parents, sister, my grandmother and last but not the least, thanks to all my patients.