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Original Research Article

Impact of perioperative period on disease-free survival among carcinoma ovary patients treated with the interval cyto-reductive surgery at a tertiary cancer centre in Kerala, India: a retrospective study

Adarsh Dharmarajan[1], Vinin N. V.[2]*, Chandran K. Nair[3], Sanjay Badesara[4], Kalaiselvi Selvaraj[5], Priya Rathi[6]

[1]Department of Surgical Oncology, [2]Department of Radiation Oncology, [3]Department of Clinical Hematology, Malabar Cancer Centre, Thalassery, Kerala, India
[4]Department of Community Medicine, All India Institute of Medical Sciences, Nagpur, Maharashtra, India
[5]Department of Community Medicine, Kasturba Medical College, Mangalore, Karnataka, India
[6]Department of Research Academy for Public Health, Kozhikode, Kerala, India

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***Correspondence:**
Dr. Vinin N. V.,
E-mail: vininnair@gmail.com

ABSTRACT

Background: Global incidence of ovarian malignancies is 300,000 as per GLOBOCAN 2018. The treatment protocol for advanced ovarian malignancies (stage IIIc and stage IV) includes neo-adjuvant chemotherapy and surgery followed by adjuvant chemotherapy. Aims of the study was to determine the effect of duration of chemo interruption on disease free survival of ovarian malignancies treated by interval cytoreduction followed by surgery.
Methods: A total 48 patients were studied for events such as recurrence, death, patient's status on last follow up, peri-operative period between 3rd cycle of chemotherapy and 4th cycle of chemotherapy. Based on the median duration of peri operative period patients was classified as early or delayed receivers of adjuvant chemotherapy. Difference in duration of over-all survival and disease-free survival was analysed through Kaplan Meier survival analysis using log-rank test. Hazard ratio adjusted for background characteristics such as staging, performance status, grade of tumour were analysed using cox proportional hazard model.
Results: The two peri operative period categories based on mean value (85 days) didn't show any significant association to disease free interval (minimum-21days, maximum-146 days, Hr = 1.3, p-value = 0.52). Other established factors like stage, extent of resection, response to chemotherapy, also didn't show any significant association. Serum marker level showed a significant negative correlation with disease free survival (minimum-9 days, maximum-30659, p-value =.04, Hr = 3.19).
Conclusions: The study could not establish any correlation between peri operative period and median disease-free survival. The small sample size is a limiting factor, well controlled randomized trials may need for further clarification.

Keywords: Disease-free survival, Ovarian malignancy, Perioperative period

INTRODUCTION

Ovarian malignancy is the most common cause of death due to gynaecological malignancy among women in

developing countries.[1] As per the globocan international agency for research on cancer on 2018, ovarian malignancy is the eight most common malignancy among women and the annual incidence of ovarian malignancy is over 300,000 globally.[1] Around 75% of the patients will be at stage iii at the time of diagnosis.[2] Upfront surgery is not possible in all advanced staged cases (stage IIIC and stage IV) due to location and volume of disease, co morbidities and poor performance status. In such patients the recommended protocol is, three cycles of neo-adjuvant chemotherapy at regular interval of 3 weeks followed by, surgery and 3 cycles of adjuvant chemotherapy.[3] Even though recommended treatment protocol offers 75% clinical remission; the average disease-free survival ranges from 16 to 21 months.[2]

Peri-operative period is the period from last date of neo adjuvant chemotherapy to the resumption of adjuvant chemotherapy. It can get altered due to multiple reasons like complications due to chemotherapy, post-surgical complications, long waiting list and other co morbidities. This can lead to chemo resistance and may affect the clinical outcome of the disease, which can be measured by disease free survival.[4] This study will assess the effect of peri operative period on disease free survival in advanced ovarian cancer patients undergone interval cytoreductive surgery.[5] Other well predicted variables affecting disease free survival are age, r-status (extend of resection), histopathology, stage of the disease, grade of the disease, and presence of ascitis, serum marker leve.[4] CA125 is a glycoprotein first described by Bast et al.[6] CA125 ovarian is not specific to ovarian cancer and is widely distributed in adults tissue.[7,8] The widely adopted cut off value of 35 kilo units/litre is based up on the distribution of values in healthy subjects when 99% of 888 men and women were found to have levels below 35 kilounits/litre.[9] In post-menopausal women CA125 levels tend to be lower than general population.[10-12] Levels in white women have been found to be higher than in African/Asian women.[13] It can also elevated in other malignancies such as pancreatic, breasts, colon and lung cancer.[8,10]

Approximately 85% of patients with epithelial ovarian cancer have CA125 levels of greater than 35 kilounits/litre with elevated levels found in 50% of the patients with stage 1 disease and more than 90% of the patients with stage II to stage IV disease.[8,9,14] CA125 levels are less frequently elevated in mucinous and border line tumors compared to scrous tumors.[8,15,16] CA125 can be elevated in the pre-clinical asymptomatic phase of the disease.[11] Although 47% of non scrous type of cancers developed in the setting of elevated CA125 level between 35 and 65 kilounits/litre, 75% of the scrous ovarian cancers developed when the CA125 levels were normal (< 35 kilo units/L). In post-menopausal women an elevated CA125 in the absence of ovarian cancer has been found to be a risk factor for death from other malignant disease.[17]

Pre-operative serum CA125 levels frequently reflect the volume of disease and do not appear to have an effect on survival. However, post-operative CA 125 levels, both during and after completion of first line chemotherapy have prognostic value.[18,19] Some investigators have demonstrated that the normalization of serum CA125 levels after 3 cycles of chemotherapy is associated with more favourable outcome, as well as achievement of CA125 nadir of $\leq$ 10 units/mL up on completion of the treatment.[18,19] Although this information has prognostic significance it has limited therapeutic value in the absence of effective salvage regimens with curative potential.

Post-operatively, the ca125 level provides a sensitive way to monitor treatment response and development of disease recurrence. Hence, in this study we assess the effect of duration of peri-operative period in carcinoma ovary patients on prognosis who underwent interval cytoreductive surgery.

METHODS

This was a retrospective cohort study conducted in tertiary rural cancer care centre at in South India and the patients enrolled during the reference period of January 2012 to January 2018. It offers oncology treatment for patients from North Kerala, Mangalore and Puducherry. Study was conducted in division of gynaec-oncology in the department of surgical oncology. Annually, 75 carcinoma ovary cases got registered in this department for management. All patients fulfilling the eligibility criteria who have undergone the procedure during the study period was included. Around 200 advanced epithelial carcinoma pateints are registered in the study setting for management.

Inclusion criteria

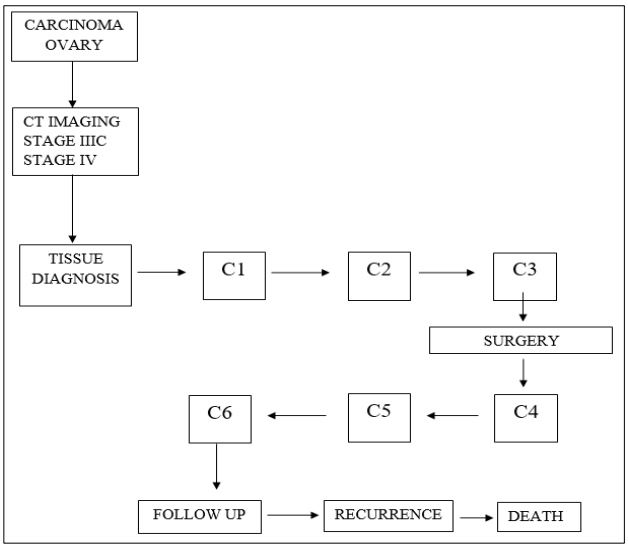
- Advanced stage (stage III and stage IV) ovarian cancer patients completed neo-adjuvant chemotherapy and underwent interval cyto reductive surgery within the study period.

Exclusion criteria

- Ovarian cancer patients who underwent primary cytoreductive surgery.

After initial tissue diagnosis patients underwent neo adjuvant chemo therapy; further, three cycles of carboplatin (AUC 5), paclitaxel (175 mg/m^2) at a regular interval of 3 weeks followed by surgery and adjuvant chemo therapy. Patients followed at regular interval. Events such as recurrence, death, patient's status on last follow up were systematically recorded in the case sheet (Figure 1).

Data on patient demographic, clinical characteristics and outcome were captured in structured data extraction sheet.



C1: Initiation of 1st day of 1st cycle of chemotherapy, C2: Initiation of 1st day of 2nd cycle of chemotherapy, C3: Last date of 3rd cycle/date of completion of neo-adjuvant chemotherapy, C4: Initiation of 1st day of 4th cycle of chemotherapy, C5: Initiation of 1st day of 5th cycle of chemotherapy, C6: Date of completion of last cycle of chemotherapy

Figure 1: Patient flow of management for advanced epithelial carcinoma in Malabar Cancer Centre, Thalassery, Kerala, India.

Continuous variables such as age, BMI and serum marker CA125 was summarized as mean (SD). Clinical staging, co-morbidities, grade of tumour, performance status, and chemo response were summarized in terms of frequencies and percentages. Outcome considered among advanced ovarian malignancy in this study was overall survival after initiation of treatment and disease-free survival after initiation of chemotherapy. Duration of survival and disease-free survival was summarized as median. Based on the treatment calendar peri-operative period between 3rd cycle of chemotherapy and 4th cycle of chemotherapy was derived. Based on the median duration of peri operative period patients was classified as early or delayed receivers of adjuvant chemotherapy. Difference in duration of over-all survival and disease-free survival was analysed through Kaplan Meier survival analysis using log-rank test. Hazard ratio adjusted for background characteristics such as staging, performance status, grade of tumour was analysed using cox proportional hazard model.

Statistical analysis

Information recorded in data extraction proforma was entered in epidata after double entry and validation process, data was analyzed using epidata analysis software version 3.1 for entry and version 2.2.2.178 for analysis (epidata association, odense, Denmark) software.

RESULTS

The total number of 46 patients with advanced carcinoma ovary were included in this study. In this cohort 19 (41.3%) of them had co morbidities and diabetes was the major one 14 (30.4%). Most of them had performance status 1-3 (76%) (Table 1).

Table 1: Characteristics of the patients underwent chemo reductive surgery for ovarian carcinoma in Malabar Cancer Centre from January 2012 to January 2018.

Factor	Number	%
Clinical stage at the time of diagnosis		
Stage IIIc	29	63
Stage IV	17	37
Histological type of malignancy		
Serous	44	95.7
Mucinous	2	4.3
Clear cell	0	0
Endometriod	0	0
Transitional cell	0	0
Disease grade		
High	43	93.5
Low	3	6.5
Ascitis		
Yes	34	73.9
No	12	26.1
Extend of post-surgical resection		
R0	43	93.5
R1	3	6.5
R2	0	0
Chemo response		
Partial response	37	80.4
Complete response	9	19.6
Comorbidities	19	41.3
DM	14	30.4
HTN	12	26.1
PST		
1	35	76
2	9	19.6
3	2	3
Recurrence	16	34

DM: Diabetes mellitus, HTN: Hypertension, PST: Performance status

Table 2: Characteristics of the patients underwent cyto reductive surgery for ovarian carcinoma in Malabar Cancer Centre from January 2012 to January 2018.

Factor	Mean (SD)
Age in years	52.6 (8.6)
Serum CA-125 IU/ml*	1157 (256.5-3494.8)
BMI (kg/m^2)	25.0 (8.1)
POP	80.0 (27.3)
DFI*	525 (243-843)

*Median (IQR), CA: Carcinoma antigen, BMI: Body mass index, POP: Perioperative period, DFI: Disease free interval.

The mean age in the study group is 52.6 and mean BMI 25 (Table 2). Laboratory evaluation showed a wide range of serum marker CA 125 level with a median value of 1157 IU (256.5-3494.75) (Table 2). Most of the patients were stage III: 29 (63%) at the time of diagnosis and belonged to high grade 43 (93.5%), serous 44 (95.7%) histology (Table 3). Ascitis was present in a good number of patients 34 (73.9%) at the time of diagnosis (Table 3). Majority of them underwent r0 resection 43 (93.5%) and all of them completed chemotherapy (Table 1).

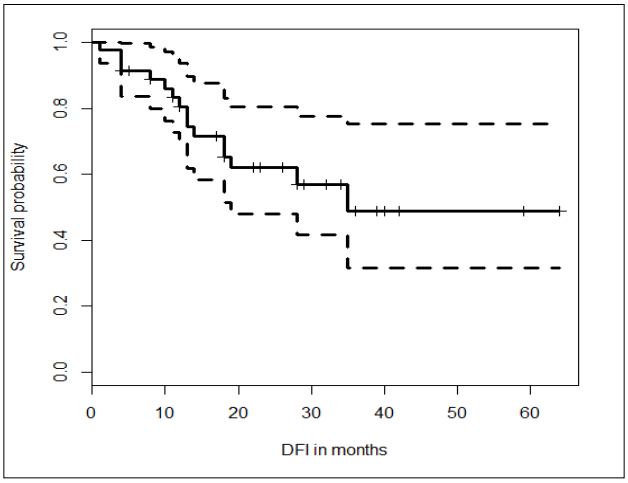


Figure 2: Disease free interval of entire cohort.

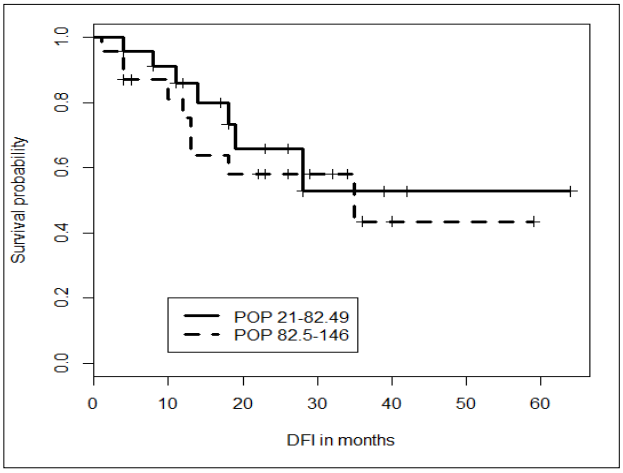


Figure 3: Comparison of DFI for two groups (Perioperative period).

Complete response was seen in 85% of the cohort (Table 3). On regular follow up 16 (35%) patients got recurrence at different intervals. The mean disease-free survival was 35 months (Table 2). The two peri operative period categories based on mean value (85 days) didn't show any significant association to disease free interval (minimum-21 days, maximum-146 days, Hr = 1.3, p-value = 0.52) (Figure 2). Other established factors like stage, extent of resection, response to chemotherapy, also didn't show any significant association. Serum marker level showed a significant negative correlation with disease free survival (minimum-9 days, maximum-30659, p-value = .04, Hr = 3.19) (Figure 3).

Table 3: Influence of prognostic factors on DFI.

Variable	Two years disease free survival %	P-value	HR (95% CI)
Ascitis			
Yes	53.3	0.34	1.85
No	64.8		
Response			
Complete	85.7	0.13	4.70
Partial	49.9		
Stage			
3	59.4	0.07	2.5
4	32.6		
Resect			
R0	59.3	0.45	1.77
R1	33.3		
Serum marker			
Marker (9-1113)	67.1	0.047	3.19
Marker (1114-30659)	34.6		
Perioperative period			
POP (21-82.49)	52.7	0.15	
POP (82.5-146)	43.5		

DISCUSSION

The main focus of this study is to validate the influence of perioperative period as a prognostic factor in carcinoma ovary patients, who underwent interval cytoreductive surgery. The mean perioperative period in our cohort is 82.5 days (Table 2). Based on this median value we divided the cohort into two groups (minimum = 21 days. Maximum = 146 days}. The median follow-up was 26 months. The disease-free survival for the entire cohort is 35 months (std. err = 0.10, ci-0.31-0.75) (Table 2). The difference in disease free survival for the two groups was analysed by Kaplan Meier survival analysis.

Comparison showed that the perioperative category with short duration has got better survival advantage than the other. But it was not statistically significant. In a retrospective study by Fathi KA they assessed the effect of chemo interruption on disease free survival and overall survival. 97 patients who were treated with neo adjuvant chemotherapy and they made a planned delay in interval cyto reduction. Cox regression analysis done to identify significant predictors of progression free and overall survival using well established prognostic factors, stratified by residual disease. The chemotherapy was interrupted for a median of 50 days. No effect was found on progression free survival by interruption to chemotherapy. But the main drawback of this study was only 50% of population underwent complete cyto reduction (R0), is an important prognostic factor.[5] In our study 95% of the population underwent complete cyto reduction.

Another study by Nagel NCI and Backes FJ on effect of delay in chemotherapy and dose reduction on progression free survival in the treatment of ovarian cancer, no difference was found in survival for those with delay or reduction of chemotherapy.[20] The limitations in their study was

- A total 35 patients were excluded from analysis since they received intra peritoneal chemotherapy
- Only 27% of study population had delay in chemotherapy.

Literature shows that CA 125 can be used in the diagnosis, response to chemotherapy, prognostication. The actual importance of CA 125 in the pre-treatment setting need to be defined in further settings. The median value of serum marker level in our cohort was 1114 IU [IQR (253-3276)]. Based on the mean value we divided the cohort into two groups (minimum = 9, maximum=34948). The disease-free survival was compared for the two group [p value = 0.04, (hr =3.19)] (Table 3). The serum marker level at the time of diagnosis showed a negative correlation with disease free survival. In a study by Moon JH, showed that CA 125 level after first cycle of adjuvant chemotherapy is strong independent prognostic factor for advanced ovarian cancer with complete response.[21]

Other prognostic factors didn't show any significant association (Table 3). Only limited data is available to compare perioperative period and disease-free survival. A small sample size is also a limitation in this study. Western literature is actually less, it may be due to efficient healthcare system, and it can exclude avoidable factors like long waiting period

CONCLUSION

This retrospective study could not establish any correlation between peri operative period and median disease-free survival. The small sample size is a limiting factor, well controlled randomised trials may need for further clarification.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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