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# A Prospective and Retrospective Study to Evaluate the Time Interval Between Surgery and Initation of Adjuvant Chemotherapy in Ovarian Cancer at A Rural Tertiary Hospital in Central India.

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**ABSTRACT:** Aim: The influence of time to chemotherapy (TTC) on recurrence and survival among epithelial ovarian cancer(EOC) patients still remain unknown. Methods: This single center retrospective and prospective cohort study was conducted on 224 EOC patients who underwent surgery followed by taxane plus platinum –based chemotherapy in the MGIMS, Sewagram, Wardha, India between 2012 and 2015 for retrospective study and 2015 to 2018 for prospective study. The multivariate cox proportional regression models were applied to calculate hazards ratios(HRs) and 95% confidence intervals (CIs) for progression –free survival(PFS) and overall survival (OS) after adjustment for potential confounders. Results: The median follow –up duration was 2.97 years (inter- quartile range from 2.11 to 4.13years). The recurrence and mortality rate of all the patients was 51.34%(115/224) and 43.3%(97/224) respectively. Having comorbidity, residual disease, ascities, and advanced FIGO stage (III-IV) was associated with worse PFS and OS of EOC patients. Compared to TTC less than 14 days, delayed TTC (more than 14 days) was associated with a worse PFS (HR=1.16; 95% CI: 0.96- 1.92) and OS (HR=1.22; 95%CI: 0.95-2.00). Notably, in EOC patients with advanced stage, delayed TTC (more than 14 days) was associated with worse PFS (HR=1.51; 95% CI: 1.02-2.24) and OS (HR=1.53; 95%CI: 1.01-2.32) when comparing to TTC less than 14 days. Conclusion: delayed TTC was associated with higher rates of EOC recurrence and less survival among these patients with advanced stage. The findings of the present study may provide evidence for gynaecologist as well as these ovarian cancer patients to make further decision for the treatment.

**KEYWORDS:** Epithelial ovarian cancer (EOC), survival, time to chemotherapy.

## I. INTRODUCTION

Malignant ovarian tumor is the second most common gynaecological cancer, accounting for 18.8% of all gynaecological cancers in developing countries and 28.7% in developed countries (1). Ovarian cancer is the eighth most common cancer among women, and it includes about 4% of all women's cancer (2). This disease has high morbidity and mortality rates among cancers of the reproductive system (3). According to global estimates 225,000 new cases were detected each year, and 140,000 people annually die from disease (2). The American cancer society has estimated that there will be 22,280 new cases of ovarian cancer and 14,240 deaths during 2016 in the United States (4). Residual disease (RD) after initial surgery, International Federation of Gynaecology and Obstetrics (FIGO) stage, tumor grade, and histologic types are well- established factors dominating the response rate to chemotherapy and survival rate of this disease (5). Platinum- based chemotherapy is routinely recommended after primary surgery aiming at complete tumor resection for advanced ovarian cancer. In routine clinical practice, a lot of discussion is focused on the optimal time from surgery to the initiation of chemotherapy in the disease, however, this question has not been well solved so far. Survival experimental studies showed that removal of the primary tumor may increase the numbers of circulating tumor cells and potentiate the growth of metastatic deposits (6-11). This increase in metastatic growth is probably due to correlation with a reduction in angiogenesis inhibitors, such as angiostatin, following surgery (6,7,11). Further- more, in vivo studies a decreased survival after a long time to chemotherapy (TTC) as increased metastatic growth after surgery was found (7,8,12). Inspite of these out coming biological evidence, the optimal time between primary surgery and initiation of the chemotherapy has been controversial in the results of published epidemiological studies (13-25). Warwick et al. (25) first reported the TTC was positively associated with overall survival (OS) on the basis of two prospective randomised phase III trials in 1995.

Subsequently, survival prospective and retrospective studies found similar positive results of aforementioned association. Hofstetter et al. (18) analysed the data of 191 patients with advanced serious ovarion cancer from a prospective multicenter study Ovarian Cancer Diagnosis and found that compared to patients who received the first cycle of chemotherapy >28 days after surgery, patients with an earlier (<28 days) start of chemotherapy had a significantly improved 3 years' survival rate of 73% after adjustment of several potential confounders. However negative findings were also found in some studies (13, 15,20,21,23,24). A most recent report from China found non- significant result whether patients were categorised into four groups by TTC quartile or two groups. Further modified by with or without RD, there were still no difference in progression – free survival (PFS) and OS (13). These variable results might be attributed to different inclusion criteria of patients, TTC category, and whether adjustment of potential confounders of these studies (26). Hence we planned prospective as well as retrospective study to evaluate the length of the interval from primary surgery to platinum based and taxal chemotherapy in relation to the quality of life and the survival of patients with EOC, at Rural tertiary care MGIMS, Sevagram, Wardha in Central India. The findings of the present study may provide evidence for Gynaecologist and these ovarian cancer patients to make further decision for the treatment.

## II. MATERIAL AND METHODS

This prospective and retrospective study was conducted at the Mahatma Gandhi Institute of Medical Sciences, (MGIMS) Sevagram Wardha India between December 2015 and December 2018 for prospective study and December 2012 and December 2012 and December 2015 for retrospective study. Patients were included if they were diagnosed as primary EOC and received taxane – plus platinum (Cisplatin or carboplatin)- based intravenous chemotherapy in both group (prospective vs retrospective group) received early post operative chemotherapy within 14 days and retrospective groups received delayed post-operative chemotherapy after 14 days (2 weeks). In contrast, patients were excluded if they underwent surgical exploration at other institution but received chemotherapy in the MGIMS hospital, received neoadjuvant therapy or non- taxane – plus platinum- based chemotherapy, received intraperitoneal chemotherapy, and were treated for recurrent disease. The ethical clearance for this study was obtained from the Institutional Ethical committee of MGIMS.TTC was defined as time interval between the primary surgery and initiation of chemotherapy. Information on demographic and clinical factors was obtained through patients electronic medical records from hospital information system of the MGIMS. Data included date and diagnosis, date of surgery, date of chemotherapy, tumor histology, tumor grade comorbidity, residual disease (RD), ascites and treatment. Tumor stage and grade was established according to criteria of the FIGO and histologic typing system of the WHO respectively. Tumours were grades as well (G1), moderately (G2), or poorly (G3) differentiated. RD was divided into either ' none detectable when none visible disease was left at the end of surgery. If visible disease was left, we classified them into '≤1 cm' and '> 1 cm' according to the size of the disease. Performance status (PS) was obtained according to the criteria of the eastern cooperative oncology group (ECOG) scale. Comorbidity, which is defined as the presence of one or more diseases in addition to the primary disease, was classified as 'yes (score ≥1) ' or 'no (score =0) 'using the charlson comorbidity index. All these after mentioned information were obtained and checked by us.

In accordance to Response Evaluation Criteria in Solid Tumours (RECIST) criteria (27), the evaluation of the clinical progression of disease was based on clinical examination, serum Ca-125 assay, chest X-ray, abdomino-pelvic ultrasound and computed tomography scan. Additional investigation were performed when required. The primary endpoint was PFS, defined as time from the completion of primary surgery to first progression or recurrence of disease or death from any cause. OS was defined as time from completion of primary surgery to death any cause or date of last follow- up for patients still alive. Cause of death was obtained from the death certificates. Descriptive statistics were used for demography and clinical characteristics across TTC categories and estimated using Mann- Whitney U test for continuous variables and Chi -squire test for categorical variables. Continuous variable was summarized as the median with inter- quartile range (IQR). Categorical variables were expressed as number with percent. The Cox Proportional Hazards Model was applied to evaluate Hazards ratio (HR) and 95% confidence intervals (CIs). TTC was categorised into group: less than 14 days (<14 days) for prospective and more than 14 days (≥ days) for retrospective group. We conducted multivariable adjusted analysis, including the following potential confounders: age at diagnosis, FIGO stage, RD, comorbidity, performance status, ascites and cancer grading. Likelihood ratio tests were conducted to examine whether the associations between TTC and PFS & OS were modified by the aforementioned potential confounders or modifiers. In sensitivity analysis, we excluded patients failed to finish six cycle of platinum based intravenous chemotherapy or patients who recurred or died within 1 year of study enrolment. All analysis was performed by SAS software (version 9.3).

## III. RESULT

During the study period from December 2012 to December 2018, a total 904 gynaecological cancer patient were admitted. Out of them 4 (0.44%) cases were vulval cancer, 6 (0.66%) cases were vaginal cancers, 632 (69.91%) cases were cervical cancer, 4 (0.44 %) of carpus uteri which included sarcoma, leiomyoma, 32 (3.53 %) cases of endometrial cancer, 224 (24.77%) cases of ovarian cancer. Other (0.44 %) including fallopian tube cancer. Therefore, overall ovarian cancer cases are increasing over the years. After application of inclusion and exclusion criteria, we had included 224 patients for analysis. Out of 224 patients, 120 patients were included in prospective group (<14 days TTC) and 104 patients were included in retrospective group (≥ 14 days TTC). The median age of these patients were 57 years (IQR :45 to 69). After a median observation of 2.97years (IQR:2.11 to4.13), 115 (51.34%) and 97(43.3%)patients were recurred and died respectively. The median interval of TTC was 10 days, the IQR was 5- 21 days.

**Table 1**: Demographic characteristics and clinical predictors of epithelial ovarian cancer patients according to time interval between surgery and chemotherapy.

| Variables | Time intervals between surgery and chemotherapy days | | P value * |
|---|---|---|---|
| | <14 days | ≥14 days | |
| **Died** | 45(46.39%) | 52 (53.61%) | |
| **Recurrent status (%)** | 120 | 104 | |
| Yes | 58 (48.33%) | 57 (54.80%) | 0.33 |
| No | 62(51.67%) | 47 (45.20%) | |
| **Histology (%)** | | | |
| Serous | 93 (77.5%) | 77 (74.03%) | < 0.054 |
| Non Sorous | 27 (22.5%) | 27 (25.97%) | |
| **Comorbidity (% )** | | | |
| No | 63(52.5%) | 58 (55.76%) | 0.62 |
| Yes | 57(47.5%) | 46 (44.24%) | |
| **Performance status (%)** | | | |
| 0 | 0 | 0 | |
| 1 | 29(24.16%) | 21(20.19%) | 0.65 |
| 2 | 64(53.33%) | 55(52.88%) | |
| ≥3 | 27(22.51%) | 28(26.93%) | |
| **FIGO stage(%)** | | | |
| I | 23(19.17%) | 25(24.05%) | |
| II | 21(17.50%) | 21(20.19%) | 0.68 |
| III | 71(59.17%) | 55(52.88%) | |
| IV | 5(4.16%) | 3(2.88%) | |
| **Residual disease (%)** | | | |
| Non detectable | 69(57.50%) | 67(64.42%) | |
| ≤ 1 cm | 27(22.50%) | 15(14.42%) | 0.29 |
| >1 cm | 24(20.00%) | 22(21.16%) | |
| **Ascites (%)** | | | |
| No | 51(42.50%) | 45(43.27%) | 0.90 |
| Yes | 69(57.50%) | 59(56.73%) | |
| **Grading (%)** | | | |
| Grade I | 5(4.17%) | 4(3.85%) | |
| Grade II | 33(27.50%) | 29(27.88%) | 0.89 |
| Grade III | 82(68.33%) | 71(68.27%) | |

*The Mann-Whitney U and Chi-square test was used for comparing continuous variables and category variables ,respectively.

**Table 2**: Demographic and clinical characteristics and progression free survival and overall survival among epithelial ovarian cancer patients.

| Variable | No./ Events | PFS HR (95% CI)+ | No./ Events | OS HR (95% CI)+ |
|---|---|---|---|---|
| **Age at Diagnosis** | | | | |
| ≤50 | 87/41 | 0.47 | 87/35 | 0.88 |
| >50 | 137/69 | 0.93 | 137/62 | |
| **Comorbidity** | | | | |
| No | 121/51 | 0.74 | 121/42 | 0.67 |
| Yes | 103/58 | | 103/53 | |
| **Histology** | | | | |
| Serous | 170/93 | 1.74 | 170/81 | 1.71 |
| Non Serous | 54/17 | | 54/15 | |
| **Performance status (PS)** | | | | |
| 0-1 | 50/25 | 1.14 | 50/20 | 1.01 |
| 2 | 119/52 | 0.83 | 119/47 | 0.73 |
| ≥3 | 55/33 | | 55/30 | |
| **FIGO stage(%)** | | | | |
| I-II | 90/22 | 0.38 | 90/17 | 0.34 |
| III | 126/79 | 0.32 | 126/70 | 0.21 |
| IV | 8/6 | | 8/7 | |
| **Residual disease (%)** | | | | |
| Non detectable | 136/49 | 0.54 | 136/39 | 0.46 |
| ≤ 1 cm | 42/28 | 0.51 | 42/26 | 0.42 |
| >1 cm | 46/32 | | 46/31 | |
| Ascites (%) | | | | |
| No | 96/55 | 1.35 | 96/52 | 1.50 |
| Yes | 128/54 | | 128/46 | |
| Grading (%) | | | | |
| Grade I | 9/4 | 0.95 | 9/3 | 0.72 |
| Grade II | 62/29 | 0.88 | 62/24 | 0.86 |
| Grade III | 153/77 | | 153/70 | |

CI, confidence interval; FIGO, HR, Hazard Ratio; OS, overall survival; PFS, progression- free survival; + HR (95% CI) for PFS and OS were estimated by using multivariable proportional Hazards models ,mutually adjusted for all other variable in the table.

**Figure 1**:Multivariable-adjusted progression –free survival curves of patients with ovarian cancer by TTC, estimated from a proportional hazards model (adjusted for age at diagnosis, International Federation of Gynecology and Obsterics, performance status, residual disease, ascites, and grading) by using a direct adjustment method. The blue line indicates the TTC less than 14 days ,and red line indicates the TTC more than 14 days. TTC, time to chemotherapy.

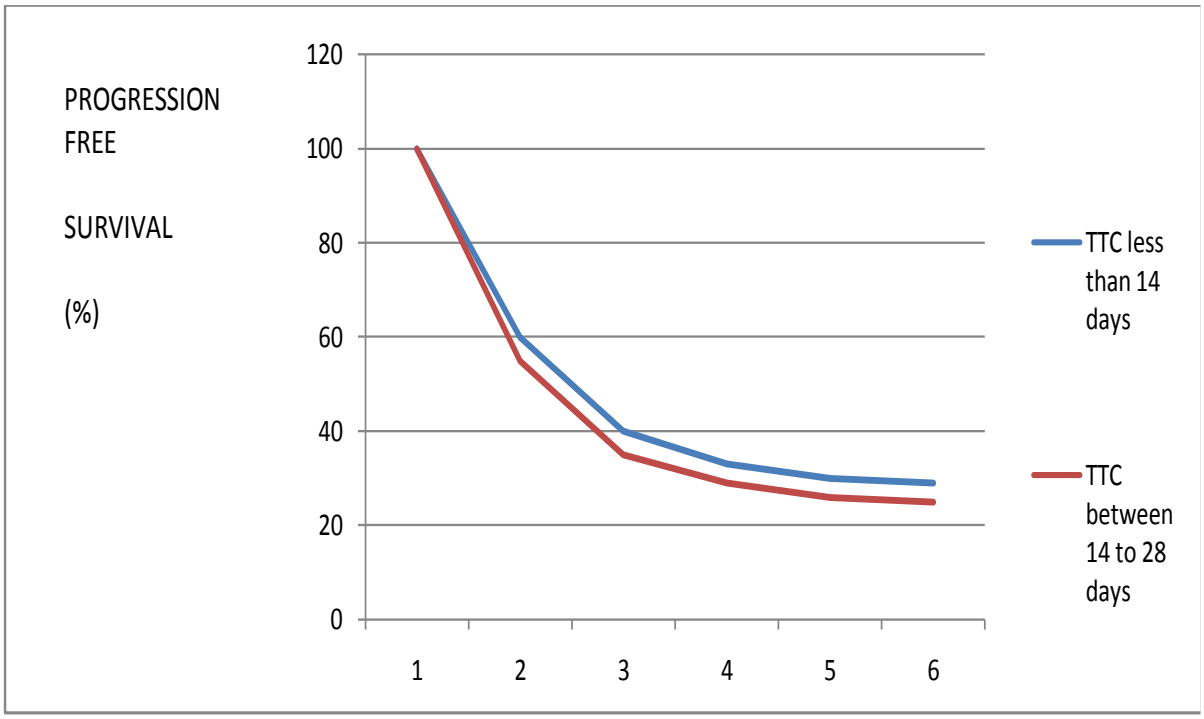
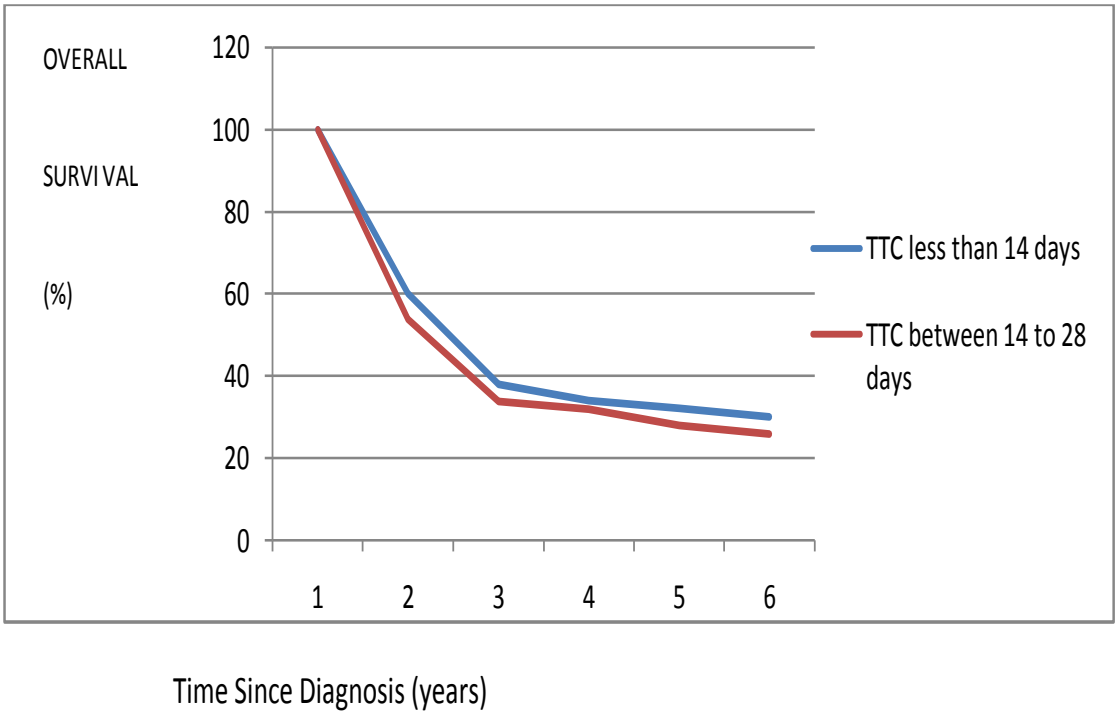



Table 1 shows the demographic characteristics and clinical pridictors of these patients according to TTC. Among these patients with delayed TTC (≥14 days), EOC patients with non- serous histology were more coomon with TTC less than 14 days ($p<0.05$). However, there was no significant difference between other demographic characteristics and clinical predictors. Table 2 concludes the selected patient characteristics in relation to PFS and OS after mutual adjustment for each other. Having comorbidity, RD, ascities and advanced stage (III– IV) was associated poor PFS and OS of EOC patients.

**Figure 2**:Multivariable- adjusted overall survival curves of patients with ovarian cancer by TTC, estimated from a proportional hazards model (adjusted for age at diagnosis, International Federation of Gynecology and Obstetrics, residual disease, performance status, ,ascites, and grading) by using a direct adjustment method. The blue line indicates the TTC less than 14 days ,and red line indicates the TTC more than 14 days.




Compared with patients with TTC less than 14 days, those with TTC more than 14 days shows an adjustment Hazard ratio (HR) for PFS of 1.16 & P for trend 0.08 (table -3, figure 1). In our interpretation some of the associations found stronger in selected subbgrops, while the directions of the associations were not changed. There was no significant interaction effect. We noted significant results in EOC patients with advanced stages (HR=0.79, p for trend <0.05). Similar patterns were found in the analysis of OS. Compared with patients with TTC less than 14 days and those with TTC more than 14 days observed an adjusted Hazard ratio (HR) for OS of 1.22 & p for trend 0.09 (table -4, figure -2). We only observed significant result in EOC patients with advanced stage (HR= 0.84, p for trend 0.42).

**Table-3**: HR (95% CI) for progression – free survival among epithelial ovarian cancer patients according to the time interval between surgery and chemotherapy.

| | Time interval between surgery and chemotherapy (days) | | P for trend | P for interaction |
|---|---|---|---|---|
| | <14 days HR (95% CI) | ≥14 days HR (95% CI) | | |
| All patients | 1.00 | 1.16 | 0.08 | |
| **FIGO Stage** | | | | |
| I-II | 0.57 | 0.79 | <0.05 | 0.36 |
| III- IV | | | | |
| **RD** | | | | |
| Non detectable | | | | |
| ≤ 1 cm | 0.93 | 1.21 | 0.29 | 0.32 |
| >1 cm | | | | |
| **Co morbidity** | | | | |
| Yes | 1.10 | 1.26 | 0.62 | 0.65 |
| No | | | | |
| **Ascites** | | | | |
| Yes | 0.73 | 0.76 | 0.90 | 0.92 |
| No | | | | |
| **Histology** | | | | |
| Serous | 3.44 | 2.85 | 0.54 | 0.58 |
| Non Serous | | | | |
| **Grading** | | | | |
| Grade1 & 2 | 0.15 | 0.13 | 0.70 | 0.76 |
| Grade 3 | | | | |

CI, confidence interval ; FIGO, international federation of gynaecology and obstetrics; HR, Hazards ratio; RD, Residual disease. + HR (95% CI) for progression- free survival was estimated by using multi variable proportional Hazards models which were adjusted for age at diagnosis , FIGO Stage , RD ,ascites and grading.

**Table -4**: HR (95% CI) for overall survival among epithelial ovarian cancer patients according to the time interval between surgery and chemotherapy.

| All patients | Time interval between surgery and chemotherapy (days) | | P for trend | P for interaction |
|---|---|---|---|---|
| | <14 days HR (95% CI) | ≥14 days HR (95% CI) | | |
| **All patients** | **1.00** | **1.22** | **0.09** | |
| **FIGO Stage** | | | | |
| I-II | 0.42 | 0.84 | <0.05 | 0.38 |
| III- IV | | | | |
| **RD** | | | | |
| Non detectable | | | | |
| ≤ 1 cm | 0.87 | 1.42 | 0.34 | 0.42 |
| >1 cm | | | | |
| **Co morbidity** | | | | |
| Yes | 1.20 | 1.57 | 0.58 | 0.62 |
| No | | | | |
| **Ascites** | | | | |
| Yes | 0.63 | 0.68 | 0.89 | 0.92 |
| No | | | | |
| **Histology** | | | | |
| Serous | 2.88 | 2.65 | 0.54 | 0.58 |
| Non Serous | | | | |
| **Grading** | | | | |
| Grade1 & 2 | 0.12 | 0.10 | 0.68 | 0.72 |
| Grade 3 | | | | |

CI, confidence interval; FIGO, international federation of gynaecology and obstetrics; HR, Hazards ratio; RD, Residual disease.

+HR (95% CI) for overall survival was estimated by using multivariable proportional Hazard model which were adjusted for age at diagnosis , FIGO Stage, RD, ascites and grading.

The PFS and OS showed robust and statistical significance. Nonlinear dose response analysis we also conducted between these patients stratified by aforementioned variables, but there was no evidence of nonlinear association between TTC and PFS and OS of ovarian cancer (data not shown).

## IV. DISCUSSION:

To our knowledge, this is one of the limited epidemiological studies reporting the association between TTC and PFS and OS of EOC patients in Asia. In this retrospective group of ovarian cancer survivors compared with patients with TTC less than 14 days (prospective group), delayed TTC (>14 days) was associated with a significantly poor PFS and OS among patients with advanced stage. This study gives to the limited evidence of the effect on survival for ovarian cancer survivors. Of many published studies, some found a benefit for early treatment initiation (14, 16-19, 25) and others failed to show an effect on survival (13, 15, 20,21, 23, 25). Among these studies with positive findings, two thirds of them are prospective designed studies. Two prospective cohart

studies found a dose-response relationship of aforementioned association( 17, 18). For example reference 17 presented the effect of TTC differed significantly for patients with or without RD on the basis of 3326 patients from three randomized phase III trials. A delay of chemotherapy by one week resulted in a 4% and 9% decrease of PFS and OS in patients with RD respectively. But delayed TTC was significantly associated with later PFS and no effect towards OS in patients with RD. In opposite, other six studies failed to find an association which might be contributed to limited sample size and different characteristics of ovarian cancer and given chemotherapy. However, the majority of these studies failed to demonstrate whether there was an interaction between clinical predictors and TTC. Inspite of previous studies generated inconsistent result, earlier TTC may improve survival through several potential biological mechanisms. Data from animal models showed that the numbers of circulating tumor cells increased as well as the growth of metastic deposits strengthened after removal of the primary tumor( 7,24,25,31-34). For example, reference detected that removal of the tumor could increase tumor growth by shuttlting of non- cycling cells in G0 phase into the cell cycle. However, reference 8 found that the earlier TTC, the more complete is the removal of the kinetic changes distant tumor foci, the more effective becomes the suppression of residual tumor burden, and the more prolong is the survival through assessment of the variation of residual tumor cell kinetics and animal survival in a murine tumor model. In addition to these, tumer cells may develop mutations that cause chemo – resistance during the TTC interval which reduces the response rate of first line chemotherapy( 35, 36). In our study we have found no effects on wound healing due to early post operative chemotherapy but it also helps in subsidence of abdominal distension due to ascitis (37).

Our study has several strengths. This is one of limited evidence from Asia investigating the association between early TTC and delayed TTC on PFS and OS of EOC patients. Additionally, the aforementioned association was assessed in a group of patient who receive homogenous treatments because of randomized controlled trials suggest that paclitaxel plus cisplatin versus paclitaxel plus carboplatin are equally effective but later group of drug is less nephrotonic ( 35,36). Further more, we carried out numerous subgroup analysis stratified by these well – established prognortic factors as well as sensitivity analysis to assess whether the main observations were robust or strong. We used restricted cubic spline function to test the nonlinearity despite no evidence was observed recently Limitations of our study include the following. Firstly, the present study is prospective as well as retrospective study that includes TTC early and TTC delayed respectively. This study dependent on accurate medical record that is based on electronic hospital information system of Mahatma Gandhi Institute of Medical Sciences, Sevagram Wardha, Maharashtra, India. Potential recall and confounding bias might exist. However, we have addressed the confounding bias by adjusted for all relevant covariates and through regression models. Secondly intraperitoneal chemotherapy has already been introduced into. Asian country like china, we included only patients received intravenous chemotherapy in the present study because the later administration is more tolerable and convenient in this country (13). Thirdly TTC can be delayed due to different situations in the clinical practice as well as due to previous guidelines for delayed TTC (22). Since we could not have expressed all these concerns in the present study of retrospective group but we have tried to clarify the benefits of early TTC through prospective groups of findings and aforementioned association. Fourthly, relatively shorter fallow- up period (mdian 2.97 years). Lastly, failure to take the first round of chemotherapy may not only decrease the survival of ovarian cancer patients but limit the interpretation of finding in younger or earlier stage of cancer patients. In view of this our prospective group of study had overcome these issues. In conclusion, our study provides evidence that ealy TTC was associated with a significantly good PFS and OS in EOC with advanced stage or delayed TTC was associated with poor PFS and OS in EOC patients with advanced stage. Further prospective studies are needed to confirm our findings as well as to guide the development of individualised policies for women with ovarian cancer in larger group of patients.

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**Figure 1**: Multivariable-adjusted progression –free survival curves of patients with ovarian cancer by TTC, estimated from a proportional hazards model (adjusted for age at diagnosis, International Federation of Gynecology and Obsterics, performance status, residual disease, ascites, and grading) by using a direct adjustment method. The blue line indicates the TTC less than 14 days, and red line indicates the TTC more than 14 days. TTC, time to chemotherapy.

**Figure 2**: Multivariable- adjusted overall survival curves of patients with ovarian cancer by TTC, estimated from a proportional hazards model (adjusted for age at diagnosis, International Federation of Gynecology and Obstetrics, residual disease, performance status, ascites, and grading) by using a direct adjustment method. The blue line indicates the TTC less than 14 days, and red line indicates the TTC more than 14 days.