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Permalink

Journal

ISSN

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Publication Date

DOI

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Peer reviewed

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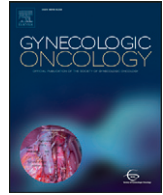
Does time interval between surgery and intraperitoneal chemotherapy administration in advanced ovarian cancer carry a prognostic impact? An NRG Oncology/Gynecologic Oncology Group study ancillary study☆,☆☆,☆☆☆

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HIGHLIGHTS

• Time from surgery to IP chemotherapy initiation (TSIC) did not impact survival.
• Gross residual disease was significantly associated with shorter TSIC.
• Gross residual disease significantly associated with higher risk of progression.

ARTICLE INFO

ABSTRACT

Objectives. To determine the relationship of the time from surgery to intraperitoneal (IP) chemotherapy (TSIC) initiation with survival of patients with stage III epithelial ovarian cancer (EOC) patients using ancillary data from cooperative group clinical trials.

Methods. Data from 420 patients with stage III EOC treated with IP chemotherapy under GOG-0114 and 172 were reviewed. The Cox proportional hazards model was used to evaluate independent prognostic factors and estimate their covariate-adjusted effects on PFS and OS.

Results. The median TSIC was 62.5 days (interquartile range 28–83). The median TSIC was longer for patients in GOG-0114 vs those in GOG-172 (83 vs 26 days, p < 0.001). TSIC was significantly associated (p = 0.049) with

Ovarian cancer
NRG Oncology

PFS: each 10% increase in TSIC (days) decreases the risk of progression by 3%. TSIC was not significantly associated with OS in this model. In a linear regression model, gross residual disease was significantly associated with shorter TSIC (R^2 −0.141, 95%CI −0.217, −0.064, p < 0.001). When only data from GOG-172 were considered, no statistical significant association was found between TSIC and PFS or OS.

Conclusions. In this ancillary data study, TSIC was not associated with improved OS in patients with stage III epithelial ovarian cancer. TSIC was significantly associated with PFS for the entire cohort, suggesting increase in PFS with longer TSIC. However, this was not found when only data from GOG 172 or GOG 114 were analyzed separately. Hence, the relationship between IP chemotherapy initiation and time from surgery needs to be studied further.

1. Introduction

Ovarian carcinoma is the leading cause of death from gynecological malignancy in the United States [1]. Advances in survival have been achieved, with the one of the longest median survival reported to date at 66 months for stage III epithelial ovarian cancer (EOC) patients treated with intraperitoneal (IP) chemotherapy [2]. However, even though there is high overall clinical response rates achieved with platinum-based therapy (up to 80%), <30% of patients will remain free of disease [3].

Evaluation of variables that could influence both progression free survival (PFS) and overall survival (OS) is imperative to achieve improvement in outcomes for EOC patients. Cytoreductive surgery has been shown to be the principal determinant of prognosis in advanced EOC [4]. Emphasis has been placed in the achievement of complete gross resection as the optimal goal of cytoreduction, for which radical surgical procedures may be required [5]. The use of radical surgical procedures to treat patients with advanced ovarian cancer has resulted in acceptable morbidity rates [6]. However, these procedures may result in prolonged postoperative recovery and delay in initiation of adjuvant chemotherapy. For this reason, time from surgery to chemotherapy initiation has been evaluated as a variable that could impact both PFS and OS.

The association of time from surgery to chemotherapy initiation with survival has been evaluated with conflicting results [7–13]. The optimal interval between cytoreductive surgery and initiation of chemotherapy has not been defined; however, most clinical trials allow delays of 6–8 weeks. Given that increased metastatic growth after tumor removal was found, in vivo studies suggest a decrease in survival after a delayed start of chemotherapy [7]. Retrospective studies have failed to show time to chemotherapy initiation as a determinant prognostic factor for advanced stage ovarian cancer [8]. An analysis of prospectively collected data from 371 women with stage IIC-IV treated with primary cytoreduction followed by platinum-based chemotherapy in Norway, also failed to show an impact of time from surgery to chemotherapy initiation on short term survival [9]. On the other hand, a recent data analysis of 3 prospective randomized phase III trials showed that early initiation of chemotherapy might result in slight improvement in survival for patients with complete cytoreduction [14]. In their analysis, Mahnner et al. found that residual tumor after surgery was associated with significantly earlier start of chemotherapy in multivariate Cox regression. Also, in patients with no residual disease after surgery, longer time to initiation of chemotherapy was associated with a trend towards earlier progression (per week delay HR 1.038, 95% CI 0.973–1.106, p = 0.257) and was associated with shorter OS (per week delay 1.087, 95% CI 1.005–1.176, p = 0.038). Tewari KS et al. recently published their results of Gynecology Oncology Group ancillary data study, in which a negative impact in survival was associated with >25 day from surgery to initiation of chemotherapy in advanced ovarian cancer [13]. All these studies indicate the need to evaluate the association of time from surgery to chemotherapy initiation further.

Although there is conflicting data, recent studies do suggest that there is a negative impact on survival by a delay in chemotherapy initiation. To date, all studies both retrospective and prospective have evaluated timing of initiation of intravenous (IV) chemotherapy. However, the effect of time to chemotherapy initiation on the prognosis of advanced-stage ovarian cancer has not been evaluated for those receiving IP chemotherapy. The optimal timing for IP catheter placement is also still under debate, especially in those patients that undergo extensive cytoreductive procedures and bowel resections. Given that IV and IP chemotherapy administration have inherent pharmacokinetic differences, the impact of timing of IP chemotherapy initiation should also be evaluated. Some of the concerns with the use of IP chemotherapy for the treatment of EOC are that there might be a delay in initiation of therapy due to performance of bowel resections. The aim of this ancillary data analysis is to review pooled data collected from GOG trials using IP chemotherapy [2,15] and analyze the time from surgery to of first-line IP chemotherapy initiation (TSIC) and its subsequent relationship with survival. As a secondary objective, we evaluated factors associated with delay in chemotherapy initiation.

2. Methods

A retrospective review of data collected from patients with EOC treated with IP chemotherapy on randomized clinical trials conducted by the GOG, protocols 114 [15] and 172 [2], was performed. Clinicopathologic and survival data were abstracted from electronic patient records from each protocol maintained at the GOG Statistics & Data Center in Buffalo, NY. All patients underwent optimal cytoreductive surgery defined as residual disease <1 cm. *TSIC* was defined as the time from surgery to initiation of IP chemotherapy, in days. Patients with incomplete data for TSIC were excluded from the study. The primary end points for both studies were progression free survival (PFS) and overall survival (OS). PFS was calculated from the date of enrollment to the date of recurrence, death or most recent follow up visit. OS was calculated from the date of enrollment to date of death or last contact. The PFS and OS of patients with different durations of TSIC were considered. TSIC was also analyzed as a categorical variable split near its median.

Both of these studies evaluated the use of IP chemotherapy for the treatment of ovarian cancer compared to traditional IV regimens (Fig. S1), but with different treatment regimens. In both trials the IV regimen consisted of IV paclitaxel 135 mg/m^2 over 24 h followed by IV cisplatin 75 mg/m^2 every 3 weeks. In GOG-0114 patients received two cycles of IV chemotherapy (Carboplatin AUC 9 IV every 28 days) prior to initiation of IP chemotherapy. Both of these trials also administered IV paclitaxel 135 mg/m^2 over 24 h on day 1 followed by IP regimen (GOG 114: cisplatin 100 mg/m^2 on day 2 every 3 weeks; GOG 172: cisplatin 100 mg/m^2 on day 2 and 60 mg/m^2 of IP paclitaxel on day 8). In order to have a higher number of patients with long term follow up and that received IP chemotherapy we used the data of both trials. We conducted the analysis for each separate trial as well, given the inherent differences in trial design,.

Categorical variables were compared between the patient subgroups by the Pearson chi-square test [16] and continuous variables by the Wilcoxon–Mann–Whitney test 1 [17]. Survival was estimated using the Kaplan–Meier method [18]. The Cox proportional hazards model

[19] was used to evaluate independent prognostic factors and to estimate their covariate-adjusted effects on PFS and OS. The nonlinearity of the effect of continuous variables was assessed using restricted cubic splines [20]. Multicollinearity was assessed through the method of variance inflation factors (VIF) described by Marquardt [21] and found unproblematic. Except where noted, all statistical tests were two-tailed with the significance level set at $\alpha = 0.05$. Statistical analyses were performed using the R programming language and environment [22] by the GOG statistical office team.

3. Results

3.1. Patient characteristics

Four hundred and forty patients received the IP chemotherapy regimen of GOG-0114 ($n = 235$) and 172 ($n = 205$). Due to incomplete data, 20 patients were excluded from this study. Data from 420 patients enrolled in the IP arm of GOG-0114 ($n = 220$) and 172 ($n = 200$) with complete TSIC values were included in this study. Table 1 summarizes the patient demographics and clinical characteristics. The median age was 57 years (interquartile range, 49 to 64), 91% were white, and 71.4% had a performance status of 0. Of these patients, 50% had poorly differentiated tumors and 70% had serous histology. Gross residual disease was found in 64% after primary cytoreductive surgery. The median TSIC was 63 days (interquartile range, 28 to 83). The median number of completed cycles of IP chemotherapy was 6 (interquartile range, 2–6).

Table 2 summarizes the similarity of clinicopathological characteristics of patients in each trial. All the patients enrolled on GOG-172 that received IP chemotherapy had a performance status of 0, while only 46% of the patients from GOG 114 had that performance status (p < 0.001). The median TSIC for patients on GOG 172 was significantly shorter than the TSIC for patients in GOG 114 (26 vs 83 days, p < 0.001). However, the median number of completed IP cycles was higher in patient treated under GOG 114 than those under GOG 172 (6 vs 4, p < 0.001).

Table 1

Eligible patient demographics and clinical characteristics (N = 420). Describes clinicopathologic characteristics of this cohort of patients.

	N
Age (years)	48.9 57.1 64.8
BMI (kg/m^2)	21.5 24.3 28.5
Race/Ethnicity	
White	91% (384)
Black	4.5% (9)
Performance status	
0	71% (300)
1	24% (99)
Grade (differentiation)	
Good	11.4% (48)
Moderate	37.9% (159)
Poor	49.5% (208)
Histology	
Serous adenocarcinoma	69.8% (293)
Endometrioid adenocarcinoma	11.7% (49)
Mixed epithelial carcinoma	8.1% (34)
Clear-cell carcinoma	4.3% (18)
Gross residual disease	
No	36% (153)
Yes	64% (267)
Surgical interval days	28 63 83
No. complete IP cycles	2 6 6
Protocol number	
GOG 114	52% (220)
GOG 172	48% (200)

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables.
N is the number of non–missing values. Numbers after percents are frequencies.

Table 2

Patient characteristics by GOG protocol (N = 420). Summarized the similarity of clinicopathologic characteristics of the patients that received IP chemotherapy under GOG 114 and those in the IP arm of GOG 172.

	GOG 114	GOG 172	p value
Age years	48.3 57.1 64.7	49.3 57.3 65.2	0.305
BMI kg/m^2	21.5 24.1 28.4	21.6 24.8 28.6	0.676
Race/Ethnicity			
White	91% (202)	91% (182)	0.062
Black	6% (13)	3% (6)	
Performance status			
0	46% (100)	100% (200)	<0.001
1	45% (99)	0% (0)	
Grade (differentiation)			0.641
Good	10.5% (23)	12.5% (25)	
Moderate	40.5% (89)	35.0% (70)	
Poor	48.2% (106)	51.0% (102)	
Histology			0.002
Serous adenocarcinoma	63% (139)	77.0% (154)	
Endometrioid adenocarcinoma	14.5% (32)	8.5% (17)	
Mixed epithelial carcinoma	9.5% (21)	6.5% (13)	
Clear-cell carcinoma	3.2% (7)	5.5% (11)	
Gross residual disease			0.296
No	34% (75)	39% (78)	
Yes	66% (145)	61% (122)	
Surgical interval days	70 83 93	19 26 36	<0.001
No. complete IP cycles	4 6 6	1 4 6	<0.001

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables.
N is the number of non–missing values. Numbers after percents are frequencies.
Tests used: 1. Wilcoxon test; 2. Pearson test.

3.2. Survival

The median PFS for the ancillary-study IP patients was 26 months. Table 3 summarizes the results of a Cox regression model of PFS fitted to the clinicopathologic variables of the study patients. In this model, TSIC is weakly associated (AHR 0.97, 95% CI 0.94–1.00, p = 0.049) with PFS and each 10% increase in TSIC (days) *decreases* the risk of progression by 3% (Fig. 1A). This result, barely statistically significant, is nonetheless surprising; however, the effect of TSIC was not significant in separate subgroup analyses of GOG-0114 and 172. Also, in this model, clear cell histology was associated with a significant higher risk of progression (AHR 2.38, 1.31–4.35, p < 0.014) as compared to serous histology. Gross residual disease was also significantly associated with higher risk of progression (AHR 1.51, 1.17–1.94, p = 0.001). TSIC is not significantly associated with OS in the Cox regression model (Fig. 1B). Gross residual disease (AHR 1.72, 1.31–2.26, p < 0.001), age (AHR 1.02, 1.00–1.03, p 0.008) and clear cell histology (AHR 3.69, 1.99–6.85, p < 0.001) were significantly associated with higher risk of death in this model (Table S1). Given the significant association of residual disease with PFS and OS, as well as the inherent differences between the trials, we evaluated if residual disease was more important in on trial versus the other. We evaluated this by incorporating the interaction term between residual disease and protocol into the survival model. We found that the interaction term was not significant, therefore, residual disease was not associated with more risk in one protocol over the other.

3.3. TSIC association with other clinicopathologic variables

In order to attempt to evaluate possible factors associated with delay in IP chemotherapy initiation we evaluated available clinicopathologic characteristics and their relationship with TSIC in a linear regression model. In this linear regression model for log TSIC as a function of the patient's baseline variables gross residual disease was associated with shorter TSIC (Table S2). Also, each 10% increase in BMI was associated with a 2% decrease in TSIC. We could not find a correlation between BMI and gross residual disease. None of the other evaluated variables,

Table 3
Multivariate Progression-Free Survival Analysis. Summarizes the results of a Cox regression model of progression-free survival (PFS) fitted to the covariate data of the study patients.

Covariate	AHR	95% CI	p[*]
Age(years)[a]	1.01	1.00–1.02	p = 0.287
BMI (kg/m^2)[b]	0.99	0.94–1.05	p = 0.824
Race/Ethnicity			
White	1.00	Referent	p = 0.321
Black	0.84	0.48–1.49	
Other	0.61	0.31–1.21	
Performance status			
0	1.00	Referent	p = 0.340
1	1.08	0.79–1.48	
2	1.46	0.88–2.42	
Grade (differentiation)			
Good	1.00	Referent	p = 0.146
Moderate	1.61	1.08–2.41	
Poor	1.48	0.99–2.19	
Not graded	1.57	0.48–5.14	
Histology			
Serous adenocarcinoma	1.00	Referent	p = 0.014
Endometrioid adenocarcinoma	0.70	0.47–1.05	
Mixed	1.05	0.69–1.60	
Clear-cell carcinoma	2.38	1.31–4.35	
Other	1.01	0.64–1.58	
Gross residual disease			
No	1.00	Referent	p = 0.001
Yes	1.51	1.17–1.94	
TSIC (days)[c]	0.97	0.94–1.00	p = 0.049

[a] The AHR denotes the change in risk of progression or death associated with an increase of 1 year of age.
[b] The AHR denotes the change in risk of progression or death associated with a 10% increase in BMI (kg/m^2).
[c] The AHR denotes the change in risk of progression or death associated with a 10% increase in TSIC (days).
[*] The p-values are from the overall test of significance of each covariate in the model.

such as age, performance status, or histology, were noted to be significantly associated with TSIC. However, other interesting variables such as radicality of the surgery or postoperative complications were not able to be evaluated given lack of data.

3.4. GOG 172 analysis

Given that GOG 114 required administration of 2 cycles of IV carboplatin prior to beginning of IP therapy, which could confound the analysis of TSCI, independent analysis of GOG 172 and GOG 114 data was performed. This data was analyzed as a continuous variable for both trials and as categorical variable for GOG 172, dichotomizing the data by those who received IP chemotherapy within 25 days and those who received it in or after 25 days from the surgery (the median

was 26 days). Table 4 summarizes the patient demographics and clinical characteristics. The proportion of patients that had residual disease was significantly higher in those who received the first cycle of IP <25 days from surgery than those that received ≥25 days (69.8% vs 54.4%, p = 0.27).

There was no association of TSIC with survival, PFS (HR 0.748, 0.53–1.04, p = 0.086) or OS (HR 0.878, 0.62–1.25, p = 0.470) (Fig. S2). The only variable significantly associated with TSIC in the linear regression model was presence of gross residual disease, with shorter TSIC seen in those patients with residual disease (HR −0.263, −0.42 to −0.11, p < 0.001). When analyzed as a categorical variable, there was not an association of TSIC with survival, PFS (p = 0.22) or OS (p = 0.52) (Fig. 2). This result was maintained when TSIC was analyzed as quartile intervals as well. As for the entire cohort, the only variable that was significantly associated with survival was residual disease after surgery in the patients that received IP chemotherapy as part of GOG 172 (AHR 1.98, 1.33–2.96, p < 0.001) (Table S3, online).

3.5. GOG 114 analysis

Given that patients in GOG 114 received 2 cycles of high dose carboplatin IV (AUC 9) prior to the initiation of the IP chemotherapy, we also analyzed this trial separately. We first wanted to evaluate if there was a relationship between the time to initiation of the IV carboplatin and both PFS and OS. We noted that time to initiation of IV carboplatin was not significantly associated with either PFS or OS (p = 0.64 and 0.87, respectively). We also analyzed the relationship between time to initiation of IP chemotherapy (TSIC) in this group. The TSIC for this group was also not significantly associated with PFS or OS.

4. Conclusion

IP chemotherapy has been shown to provide the longest survival to date for patients with stage III epithelial ovarian cancer with no gross residual disease (127 months in patients with no gross residual disease treated with IP on GOG 172) [24]. However, despite the clinical announcement encouraging the use of IP chemotherapy in these patients by the National Cancer Institute (NCI) in 2006, this modality has not been widely adopted. Wright et al. reported that fewer than 50% of eligible patients treated at six comprehensive cancer centers in USA received IP chemotherapy [23]. They also showed a significant improvement in overall survival in those patients treated with IP vs IV chemotherapy (3 year OS 81% vs 71%, HR 0.66, 95% CI 0.47–0.92, p = 0.02). Hence, further investigation on factors affecting adoption of this modality is warranted.

Since there is no consensus on the timing of IP catheter placement or initiation of IP chemotherapy, especially in those patients undergoing
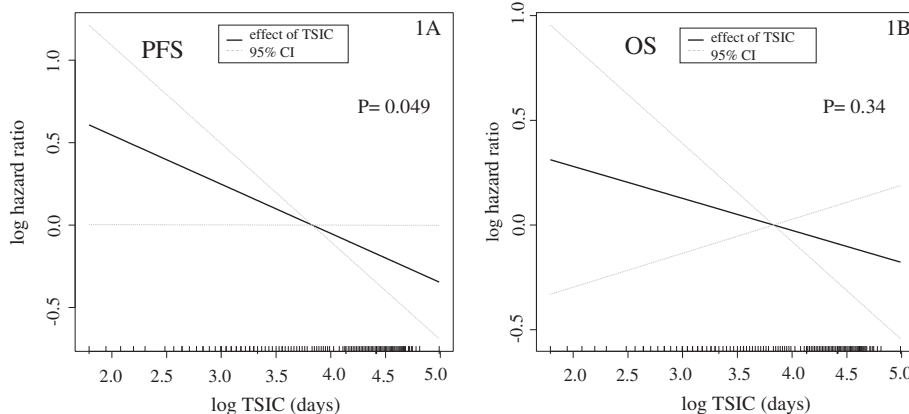
Fig. 1. Plot of the partial effect of TSIC on the log hazard ratio of the progression-free (1A) and overall survival models (1B) in GOG 114 and GOG 172. These are the plots of the partial effect of log TSCI on the log hazard ratio of PFS (1A) and OS (1B) models, respectively. They represent the risk contribution of continues variables (TSCI) in a survival model.

Table 4
Eligible patient demographics and clinical characteristics GOG 172. Summarizes the similarity of clinicopathologic characteristics of the patients that received IP chemotherapy under IP arm of GOG 172 prior to 25 days from surgery and those that received it in or after 25 days from surgery.

	<25 N = 86	≥25 N = 114	Test statistics
Age (years)	49.3 59.9 66.4	49.4 55.2 64.6	p = 0.3331
BMI (kg/m^2)	22.8 25.6 29.1	21.0 24.0 28.3	p = 0.0771
Race/Ethnicity			p = 0.8832
White	91.9%	90.4%	
Black	2.3%	3.5%	
Performance status			p = −2
0	100% (86)	100% (114)	
1	0% (0)	0% (0)	
Grade (differentiation)			p = 0.5572
Good	15.1% (13)	10.5% (12)	
Moderate	31.4% (27)	37.7% (43)	
Poor	51.2% (44)	50.9% (58)	
Histology			p = 0.8222
Serous adenocarcinoma	76.7% (66)	77.2% (88)	
Endometrioid	9.3% (8)	7.9% (9)	
Mixed	4.7% (4)	7.9% (9)	
Clear-cell carcinoma	5.8% (5)	5.3% (6)	
Gross residual disease			p = 0.0272
No	30.2% (26)	45.6% (52)	
Yes	69.8% (60)	54.4% (62)	
No. completed IP cycles	1 3 6	1 5 6	p = 0.4811

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables.
N is the number of non–missing values.
Numbers after percents are frequencies.
Tests used: 1. Wilcoxon test; 2. Pearson test.

aggressive cytoreduction, TSIC is a variable that should be investigated. In our study, time from surgery to initiation of IP chemotherapy (TSIC) was not associated with improved OS in patients with stage III epithelial ovarian cancer. However, TSIC was significantly associated with PFS for the entire cohort, suggesting a decrease risk of progression with longer TSIC (p = 0.049). This relationship between PFS and TSIC is contrary to the hypothesis that a delay in initiation of adjuvant chemotherapy may lead to increase tumor growth and, therefore, worse outcomes. This finding may be due to differences between GOG 114 and GOG 172, given that 2 cycles of IV chemotherapy were administered prior to IP on GOG 114. Patients in GOG 114 started IP chemotherapy significantly later than those patients in GOG 172. Therefore, we decided to conduct the analysis for each trial separately. No association was found for either OS or PFS when only data from GOG 172 or GOG 114 were analyzed. However, the proportion of patients with residual disease was higher in those patients that started IP chemotherapy prior to 25 days in the GOG 172 group. This difference may be a confounder in our study. We also evaluated the possible relationship between the time from surgery

to initiation of the first IV chemotherapy in GOG 114 and survival. Again, no association was found for either OS or PFS and time of chemotherapy initiation. Hence, there may be other confounders unaccounted for that could explain the findings for PFS when the entire cohort was analyzed.

"We found that TSIC was shorter in those patients with residual disease. This could be due to many different factors. For example, patients with less radical surgery could have undergone less radical surgery and therefore started chemotherapy sooner. However, given the available data we cannot explain it with certainty. One limitation of the trial is that we were not able to evaluate factors such as radicality of the surgical procedure performed, amount of tumor burden prior to surgery (that will in part account for tumor biology), or postoperative complications. These data were not collected in the studied trials, therefore not available for review. Such variables could be related to TSIC. They could also represent confounders present within each trial as well as in the entire cohort as a hole".

For the entire cohort, as well as for the patients treated on either trial, the most important variable for survival, both PFS and OS, is residual disease. This parameter is likely of greater importance for patients treated with IP chemotherapy, given that the penetrance of the drugs is limited to a few millimeters. Residual disease might limit the effectiveness of this adjuvant regimen. Since the administration of IV chemotherapy in GOG 114 prior to the IP regimen could reduce the tumor burden, potentially modify the efficacy of the IP therapy and the impact of residual disease on survival, we analyzed the trials separately. In our analysis residual disease was not associated with more risk in one trial over the other. Therefore, presence of residual disease most likely is also related to other variables such as initial tumor burden and tumor biology.

In contemporary practices, some practitioners start with IV chemotherapy and then transition to IP chemotherapy. This is partially due to concern that awaiting for post op recovery or placement of IP catheter might increase risk of progression and decrease survival. Our results do not support this strategy, since no association between survival and TSIC was found. Further studies would be required to clarify the role of such strategy".

Recent results of GOG 252 presented at the annual meeting of the Society of Gynecologic Oncology don't show an advantage in PFS with IP chemotherapy, however conclusions of the value of IP chemotherapy maybe premature. Given the OS of 127 months reported on patients with no gross residual disease treated with IP regimen on GOG 172 [24], the utilization of this regimen should still considered in this patient population.

Further studies are warranted to better elucidate the association between survival and TSIC. Our study is the first investigating this variable for IP chemotherapy administration, however, it is an ancillary data study of two prospective clinical trials. These trials were not designed
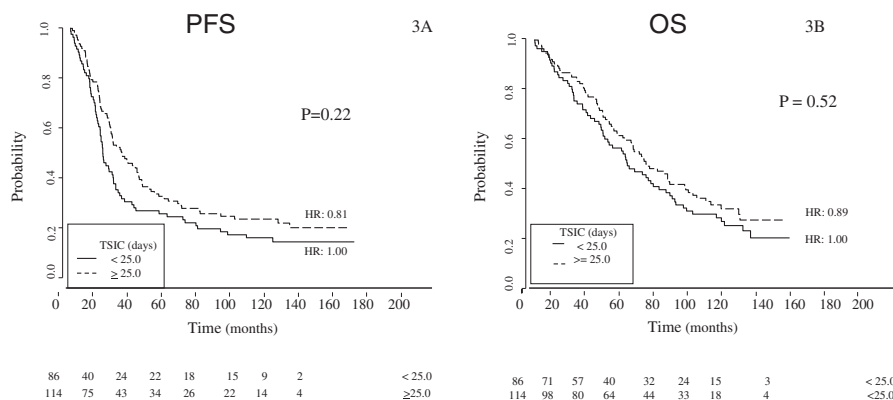
Fig. 2. Kaplan–Meier curves of progression-free (2A) and overall (2B) survival for study patients from GOG-0172, stratified by TSIC groups. The TSIC groups are those patients that received IP chemotherapy under IP arm of GOG 172 prior to 25 days from surgery and those that received it in or after 25 days from surgery. Figures below months indicate the numbers of patients at risk. The p-value is from the Wald test to compare hazard ratios between the subgroups in the multivariate model.

to answer this question and, therefore, the study might not be powered to detect a small difference in outcomes. However, the data used for the study was prospectively collected and included a large number of patients treated in multiple institutions. Our results suggest that the IP chemotherapy benefit is independent of time from surgery to its initiation. Therefore, IP chemotherapy should be considered even to those patients with no gross residual disease that may require delayed insertion of the IP catheter for adjuvant treatment initiation.

Conflicts of interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2016.10.003.

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