Title - Predictors of progression free survival, overall survival and early cessation of chemotherapy in women with potentially platinum sensitive (PPS) recurrent ovarian cancer (ROC) starting third or subsequent line(≥3) chemotherapy – the GCIG Symptom Benefit Study (SBS)

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Contribution of authors

FR contributed to the research proposal, concept development, data analysis, interpretation of results, drafted and revised the manuscript.

RO and LB contributed to data analysis, interpretation of results and contributed to revisions of the manuscript.

FJ, AL, FH, LB, AO, EL, JB, TF, JL and CR contributed to patient recruitment to the study, data analysis, interpretation of results and contributed to revisions of the manuscript.

MR contributed to the research proposal, concept development, data analysis, interpretation of results and manuscript revisions.

MF contributed to patient recruitment to the study, research proposal, concept development, data analysis, interpretation of results and revisions of the manuscript.

Conflict of Interest statement

MF has received advisory board honoraria from Astra Zeneca.

FJ has declared support/advisory conflicts of interest with Roche, Tesaro, Janssen, Astra

Zeneca, BMS, Astellas, Pfizer, Sanofi and Ipsen.

The other authors have no other conflict of interest to declare.

Abstract

Background

Potentially platinum sensitive recurrent ovarian cancer (PPS ROC) is defined by a platinum-free interval of >6 months, and usually treated with platinum-based chemotherapy with variable response and benefit in women who have had 3 or more lines of chemotherapy(≥3). We identified baseline characteristics (health-related quality of life[HRQL] and clinicopathological factors), associated with PFS, OS and early progression (within 8 weeks). The goal is to improve patient selection for chemotherapy based on a nomogram predicting PFS.

Methods

HRQL was assessed with EORTC QLQ-C30/QLQ-OV28. Associations with PFS and OS were assessed with Cox proportional hazards regression. Variables significant in univariable analysis were included in multivariable analyses using backward elimination to select those significant. Associations with stopping chemotherapy early were assessed with logistic regression.

Results

378 women were enrolled, with median(m)OS and PFS of 16.6 months and 5.3 months, respectively. The majority had ECOGPS 0-1. Chemotherapy was stopped early in 45/378 participants (12%); with mOS 3.4 months (95% CI: 1.7-7.2). Physical function(PF), role function(RF), cognitive function(CF), social function(SF), Global Health Status(GHS) and abdominal/GI symptoms(AGIS) were significant univariable predictors of PFS($p<0.030$). SF remained significant after adjusting for clinicopathological factors; $p=0.03$. PF, RF, CF, SF, GHS and AGIS were significant

univariable predictors of OS ($p<0.007$); PF, RF, SF and GHS remained significant predictors of OS in multivariable models; $p<0.007$. Poor baseline PF and GHS were significant univariable predictors of stopping chemotherapy early ($p< 0.007$) but neither remained significant after adjusting for clinicopathological factors.

Conclusion

Baseline HRQL is simple to measure, is predictive of PFS and OS and when used in conjunction with clinicopathological prognostic factors, can assist with clinical decision making and treatment recommendations for women with PPSROC≥3.

Introduction

Ovarian cancer is the leading cause of death from gynaecological cancers in the western world. Most patients have advanced stage disease at diagnosis and more than 80% experience disease recurrence after surgery and first line chemotherapy, and are offered further chemotherapy. Patients diagnosed with recurrent disease >6 months after completing platinum-based chemotherapy are categorised as having platinum-sensitive ovarian cancer and are typically offered further treatment with a platinum-based regimen with an expected median overall survival of 24-36 months.[1, 2] The duration of PFS following second and subsequent lines of chemotherapy is usually significantly shorter than the PFS with first line treatment. Most patients will be offered further chemotherapy at progression after 2nd and subsequent lines of chemotherapy, but the likelihood of clinical benefit and the duration of benefit becomes progressively less with each relapse. This is best illustrated by an analysis of over 1600 patients with recurrent ovarian cancer which showed that the median overall survival times after the 3rd, 4th and 5th relapse were 9, 6 and 5 months, respectively. Indeed, the authors suggested that patients with ROC should not have more than 3 lines of chemotherapy because of their poor prognosis.[1] Notwithstanding these recommendations, this is a difficult decision in clinical practice and many, if not most, patients are treated with multiple lines of chemotherapy, particularly those who are thought to have potentially platinum sensitive (PPS)ROC. It is difficult to identify the subgroup of patients who are likely to benefit from further chemotherapy after multiple recurrences, and distinguish them from those who have a very poor prognosis with little to gain from further chemotherapy. This remains a clinically challenging decision, and the ability to identify patients with a poor prognosis would improve patient–doctor communication regarding the role of further chemotherapy and support decision making and treatment recommendations.

There are no established predictors that can be used to reliably enable clinicians to select patients with PPSROC who have had three or more lines of chemotherapy (PPSROC≥3) who are more likely to respond to further therapy, apart from possibly BRCA mutation status.[3, 4] Similarly, there are no established reliable predictors to identify the subgroup of patients with a short survival in whom further chemotherapy is likely to be futile apart from possibly performance status. The clinical definitions of "platinum-sensitive" and "platinum-resistant" were originally derived in patients at first recurrence, but over time have become more widely and liberally used throughout the disease trajectory to characterise patients . There is uncertainty about how best to define platinum-sensitivity in patients after multiple lines of treatment, particularly given the various methods of detecting and diagnosing recurrence including CA125, imaging with computerised tomography or positron emission tomography, and symptoms.

The aim of this study was to determine whether it was possible to identify baseline predictors of progression-free survival, overall survival, and of stopping chemotherapy early (within 8 weeks) in patients with PPS ROC≥3 prior to starting chemotherapy. The ultimate goal being to identify the subset of patients with a particularly poor prognosis and a short survival in whom supportive care would be a better option than chemotherapy. We have previously reported that low baseline global health status (GHS), role function (RF), physical function (PF), and high abdominal/gastrointestinal symptom score (AGIS) were associated with worse outcomes in patients with platinum-resistant ovarian cancer.[5, 6] We considered a range of clinicopathologic characteristics previously shown to have prognostic significance at baseline in patients with PPSROC≥3, including performance status (PS), neutrophil lymphocyte ratio, thrombocytosis[7-10], aspects of HRQL, and symptoms. We developed a prognostic nomogram that could be used for patient stratification in clinical trials as well as have clinical

application and help support doctor patient communication regarding further palliative chemotherapy pending validation in the future in an independent data set.

Methods

The GCIG SBS is a prospective, observational, cohort study that enrolled adult women with platinum-resistant or -refractory ovarian cancer, and women with PPSROC about to start a third or subsequent line of chemotherapy. This latter group form the basis for the analyses in this study. Participants were able to complete HRQL questionnaires without assistance, had a life expectancy of at least 3 months, and an ECOG PS of 0-3 before starting chemotherapy. Women were enrolled from 11 countries: Australia, New Zealand, Canada, France, Germany, Ireland, Italy, Japan, Sweden, United Kingdom and United States of America.

The type, doses, duration, and frequency of administration of chemotherapy were at the discretion of the treating physician, and all supportive treatments and concomitant medications were according to standard institutional practice. All patients were considered suitable for further chemotherapy and were recruited before starting chemotherapy.

The Study was coordinated by the NHMRC Clinical Trials Centre, University of Sydney, in collaboration with Australian New Zealand Gynaecological Oncology Group (ANZGOG) and the GCIG Symptom Benefit Committee. The trial was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR: 12607000603415). The Study was performed in accordance to the NHMRC Statement on Ethical Conduct in Research Involving Humans and the Declaration of Helsinki. Ethical approval was obtained at all participating sites and all participants provided signed, written, informed consent.

Physician assessment of patients

Physicians assessed participants at baseline and every 3-4 weeks prior to each cycle of chemotherapy. They recorded baseline characteristics, symptoms (symptomatic ascites, cramping abdominal pain), and laboratory values including haemoglobin, lactate dehydrogenase (LDH), platelets, CA125, CA125 velocity, Eastern Cooperative Oncology Group performance status (ECOG PS), c reactive protein (CRP), albumin, neutrophil and lymphocyte counts. Tumour response was assessed at 6-8 week intervals using the same method of assessment throughout the study, at the discretion of the treating physician. Clinical benefit was classified as CA125 response, RECIST response, and/or symptomatic improvement as reported by the treating physician.

Patient-Reported Outcomes

Patients self-completed questionnaires at baseline (within 2 weeks before their first cycle of chemotherapy) and every 3 to 4 weeks before each subsequent cycle until disease progression, whichever came last. The questionnaires completed at baseline included the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ C-30)[11] and Ovarian Module (OV28)[12].

Statistical Analysis

QLQ C-30 subscales were dichotomised using cut-points recommended by Diouf et al.[13] Log-rank method was also used to find optimal cut-points. This procedure selects the cut-point that minimises the significance level of a log-rank test with comparison of two groups defined by the cut-point. The significance level is then adjusted for maximal selection.

Cut-points for abdominal/GI symptoms (AGIS) scale were derived using the lower and upper quartiles as used in a substudy of the AURELIA trial.[14] Sensitivity analyses used methods

for defining optimal cut-points. PFS and OS were analysed with time-to-event methods. Cox proportional hazards regression was used to assess univariable and multivariable associations. Clinical factors for the multivariable model were selected using backward elimination starting with candidate variables that were significant at $P<0.05$ in univariable analysis. The association between baseline aspects of HRQL (categorized) and stopping chemotherapy early (within 8 weeks) was determined using a chi-squared test. Multivariable analysis was performed using logistic regression with clinical factors selected using backward elimination starting with variables significant in univariable analysis ($P<0.05$). A nomogram for median PFS was developed based on the characteristics that were independently significant in the multivariable model. Variables selected for inclusion in the nomogram were based on a multivariable model developed with QoL domains included as continuous variables. Abdominal/GI symptom scale was a stronger predictor than social functioning and therefore was included in the nomogram. Abdominal/GI symptom scale demonstrated an independent significant linear relationship with PFS. The scale was later categorised for inclusion in the nomogram for simplification. More clinically practicable cut-points were chosen to discriminate between lower risk and higher risk groups based on reviewing the distribution.

Results

There were 378 women with PPS-ROC starting third or subsequent line chemotherapy in the GCIG SBS. They had a median age of 64 years and had been treated with a median of 3 previous lines of chemotherapy. Baseline characteristics are shown in Table 1. The median PFS was 5.3 months (4.9-6.0) and median OS was 16.6 months (14.1-20.1).

The clinicopathological factors associated with PFS included platelets ($x10^9$/L, per 100 unit increase), neutrophil: lymphocyte ≥5 vs. <5, ECOG (1 vs. 0; ≥2 vs. 0), chemotherapy-free

interval (months), response to last line of therapy (Complete response [CR] or Partial response [PR] vs. Progressive disease [PD] or Unknown [UK]; Stable disease [SD] vs. PD or UK) ($p<0.01$). After adjusting for these clinicopathological factors, Social Function remained an independent, statistically significant predictor of PFS (see Table 2).

The clinicopathological factors significantly associated with OS were presence of ascites, neutrophil lymphocyte ratio ≥5, platelets, log CA125, response to last line of chemotherapy, chemotherapy-free interval (months), ECOG PS and BMI. Physical Function (PF), role function (RF), Cognitive Function (CF), Social Function (SF), Global Health Status (GHS) and Abdominal/Gastrointestinal symptoms were significant univariable predictors of OS ($p<0.007$); PF, RF, SF and GHS remained significant predictors of OS in multivariable models after adjusting for clinicopathological factors ($p<0.041$) (see table 3).

Twelve percent of patients (45/378) stopped chemotherapy early within 8 weeks and had median PFS of 1.6 months (range 1.2-1.7) and median OS of 3.4 months (1.7-7.2). The clinicopathological factors strongly associated with stopping chemotherapy within 8 weeks were neutrophil count ≥7, neutrophil:lymphocyte >5 and ECOG performance status (all $p<0.004$). Other significant predictors in univariate analysis for stopping treatment within 8 weeks were lymphocytes ($p=0.017$), chemotherapy-free interval ($p=0.027$), platelets ($p=0.037$) and presence of ascites ($p=0.043$).

Poor PF and GHS at baseline were significant univariable predictors of stopping chemotherapy within 8 weeks ($p< 0.007$); neither remained significant in a multivariable model adjusting for clinicopathological factors (Absolute neutrophil count ≥7, neutrophil:lymphocyte≥5 and ECOG performance status)(see table 4).

Among 347 women with a good performance status (ECOG PS 0-1) at baseline (see Supplementary Table 1), GHS, PF and AGIS were significant univariable predictors of

stopping chemotherapy early ($p < 0.04$); PF remained an independently significant predictor of stopping chemotherapy early in those with good ECOG PS 0-1 in a multivariable model including absolute neutrophil count ≥7 and chemotherapy-free interval (see Table 5).

The factors included in the nomogram included presence of thrombocytosis (platelet count >450 x 109/L), neutrophil lymphocyte ratio ≥ 5, a chemotherapy free interval of <12 months, absence of CR, PR, or SD to most recent previous line of chemotherapy, a score of more than 50 for AGIS, and ECOG PS of 1 or 2 versus 0 (see Figure 2). Nomogram points for each included variable and its relative weight compared to the Abdominal/GI symptoms is shown in Table 5. Parameter estimates from the Cox Model are also shown in table 5. Points are shown for a nomogram including and excluding the Abdominal/GI symptoms. This shows the extent to which a HRQL variable (Abdominal/GI symptoms) influences the prediction of PFS compared with some of the other clinicopathological factors. Abdominal/GI symptoms had more weight compared with ECOG PS 0 vs. 1. Without inclusion of Abdominal/GI symptoms, greater weight was placed on haematological variables, in particular, platelet count. Interestingly, if Abdominal/GI symptoms was not included in the nomogram, ECOG PS 0 vs. 1 had greater weight, but ECOG PS 2 or more remained the same.

Discussion

There was significant variability in PFS and OS among the group of women with PPS-ROC starting a third or subsequent line of chemotherapy. A subset of patients appeared to have minimal benefit from palliative chemotherapy and supportive care alone might have been a preferable alternative. It is very challenging to predict survival in individual patients and many clinicians as well as patients are overly optimistic about the likely benefits of palliative chemotherapy and prognosis.[15] Identifying patients who are unlikely to benefit from further chemotherapy is difficult but there is a clear need to improve on patient selection

for palliative chemotherapy particularly in those who have had multiple recurrences of ovarian cancer. Physical Function, Role Function, Cognitive Function, Social Function, Global Health Status, and Abdominal/Gastrointestinal Symptoms were all significant univariable predictors of OS (all $p<0.007$); Physical Function, Role Function, Social Function and Global Health Status remained independently significant predictors of OS in multivariable models accounting for other clinicopathological factors (all $p<0.041$). Interestingly, only social function was prognostic for PFS after accounting for multiple clinicopathological factors. The two questions in EORTC QLQ C-30 which comprise Social Functioning ask the participant about whether their physical condition or medical treatment interfered with their family life; and whether their physical condition or medical treatment interfered with social activities. These are more general questions about a patient's functioning, and are not directly measuring a symptom such as fatigue. It is likely that these questions capture important prognostic information not already encompassed by clinicopathological variables or other HRQL domains.

Social functioning demonstrated relatively weaker associations with the clinical variables included in the nomogram compared to the other HRQL domains (not shown in the manuscript), adding further weight that the HRQL domain is measuring important information not measured by other domains and clinicopathological factors.

Twelve percent of these women with PPS ROC starting third or subsequent line chemotherapy stopped within 8 weeks of commencing treatment, and they had a particularly poor prognosis with a median PFS of only 1.6 months (range 1.2-1.7) and a median OS of 3.4 months (range 1.7-7.2). Poor self-rated Physical Function and Global Health Status at baseline were significant univariable predictors of stopping chemotherapy early (both $p < 0.007$). After adjusting for clinicopathological factors in a multivariable model, there were no significant HRQL predictors of stopping chemotherapy within 8 weeks. This may be due

in part to a relatively small number of women in this group who stopped treatment within 8 weeks (n=45). Importantly, in patients rated by clinicians as having good performance status (ECOG 0-1), GHS, PF, and AGIS were significant univariable predictors of stopping treatment early (all $p<0.043$), and PF remained a significant predictor in a multivariable model accounting for other clinicopathological factors ($p=0.04$).

Conflicting findings on significant prognostic factors in women with recurrent ovarian cancer have been reported in the literature, mainly due to small sample size and/or heterogeneity of population included in the different analyses.[8, 16-19] Some studies were based on clinical trials published decades ago and may be less applicable today.[8] To our knowledge, there have been no analyses published investigating prognostic factors to identify patients with PPSROC≥3 who are likely to stop chemotherapy early due to rapid progression. We have addressed this question for women with platinum-resistant ovarian cancer and found that PF and RF remained significant predictors of stopping chemotherapy early; poorer PF, RF, GHS and worse AGIS were independent predictors of shorter OS; PF, RF and GHS were independent predictors of death within 30 days of chemotherapy.[5, 6] The importance of this area of research is supported by the recognition that many patients are treated with chemotherapy in their last month or two of life, which is not considered good practice. For example, a recent large European study reported that almost 20% of patients received chemotherapy in their last month of life. This study included over 15,000 women with gynaecological cancers of whom 51%, 42%, 25%, 15% and 10% were treated with chemotherapy in their last 3 months, 2 months, 1 month, 2 weeks, and 1 week of life, respectively. The authors also noted that patients with ovarian cancer were more likely to be treated in the last months of life than patients with other cancers.[20] The authors commented that “the use of validated prognostic scores to identify patients that are the least

likely to benefit from chemotherapy would be an important step to reduce its potential overuse close to death".[20] This is in keeping with the ASCO top 5 list of opportunities to improve quality care and value published in 2012 which recommended against using chemotherapy for patients with advanced cancers that are unlikely to benefit.[21]

One in eight women with PPS ROC stopped treatment within 8 weeks despite 80% (36/45) being rated by clinicians as having good performance status before starting chemotherapy. These women also had a particularly short PFS and OS, which is even inferior to that reported in patients with platinum resistant/refractory ovarian cancer and this is despite meeting the criteria for potentially platinum-sensitive disease. Our findings suggest that patient-reported HRQL at baseline, not just clinician-rated performance status, should be considered when making decisions about treatment because aspects of HRQL were independently significant predictors of poor PFS and OS. Using this information could help inform discussions with women and their families considering chemotherapy and might temper expectations and provide a more grounded and realistic prognosis.

We studied a large number of women classified as having potentially platinum-sensitive recurrent ovarian cancer who were about to start a third or subsequent line of chemotherapy. Despite meeting the criteria for PPS ROC, this population was heterogeneous with significant variability in baseline characteristics and outcomes. To our knowledge, this is the first study to assess the prognostic significance of HRQL together with clinicopathological characteristics in this cohort of women. In particular, Abdominal/GI symptoms was shown to be strongly associated with PFS and was included in the nomogram. There was greater weight given to some of the clinicopathological variables included in the nomogram,

however, Abdominal/GI symptoms was associated with PFS more strongly than ECOG PS, and had greater weight in the resulting nomogram.

It is clear from our study, and from other reports of futile cancer treatments in the last months of life, that there is a need to develop and validate practical prognostic tools to inform clinical decision-making, guide discussions with patients and their families, and to help select and stratify participants in clinical trials. We have developed a prognostic nomogram for PFS using readily available data that could help fill this gap pending validation in other datasets. The nomogram could also be used to assess suitability and for stratification in clinical trials. It could also be used to identify patients for whom supportive care might be preferable to further anticancer treatment. This prognostic information could also be used to improve patient-doctor communication, and support decisions about the potential benefits of further chemotherapy.

The main strengths of this study are its prospective design, international participation, and large sample size of women with PPS ROC starting a third or subsequent line of chemotherapy, providing ample power to simultaneously assess multiple potential prognostic variables. Completion of HRQL questionnaires and data collection at baseline were high (96%). Our broad and inclusive eligibility criteria, and "real-world" clinical setting support the applicability of our results to routine clinical practice. However, the findings require confirmation in independent data sets.

Conclusion

Women with potentially platinum sensitive recurrent ovarian cancer commencing a third or subsequent line of chemotherapy constitute a heterogeneous group with variable outcomes. Measuring aspects of HRQL at baseline before starting chemotherapy is simple, cheap and provides important information to support individualised patient-doctor discussions regarding

the potential benefits of further therapy. Use of a prognostic nomogram in this population may help improve prognostication for the individual patient, inform discussions with patients and their families, and improve selection and stratification in clinical trials.

Table 1. Baseline characteristics of patients who had baseline HRQL questionnaire completion

Characteristic N=378	**N (%)**
Age	
<40	5 (1)
40-49	29 (8)
50-59	107 (28)
60-69	121 (32)
>70	116 (31)
Lines of previous chemotherapy	
1	2 (1)
2	150 (40)
3	108 (29)
≥4	116 (31)
Chemotherapy free interval (months)	
<6	345 (69)
6-12	101 (20)

>12	51 (10)
ECOG Performance Status:	
0	126 (33)
1	221 (59)
2	27 (7)
3	4 (1)
Cancer-related symptoms present (clinician rated)	263 (70)
Symptomatic ascites (clinician-rated)	62 (16)
Cramping abdominal pain or symptoms of intermittent/incomplete bowel obstruction (clinician-rated)	148 (39)
Response to most recent line of chemotherapy:	
CR	67 (18)
PD	116 (31)
PR	118 (32)
SD	63 (17)
UK	11 (3)
Histopathology:	
Serous	280 (75)
Other	96 (25)
Grade:	
High (includes 2 and 3)	324 (89)
Low	41 (11)
Elevated CA125	321 (90)

Table 2. Univariable and multivariable analyses of baseline HRQL domains associated with PFS (N=360)*

	Univariable analyses		Multivariable analyses**	
HRQL domain	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Global health status (<50 vs. ≥50)	1.50 (1.18 - 1.92)	0.001	1.12 (0.85 - 1.47)	0.426
Physical function (<58.3 vs. ≥58.3)	1.59 (1.26 - 2.01)	<0.001	1.14 (0.87 - 1.50)	0.346
Role function (<66.7 vs. ≥66.7)	1.33 (1.06 - 1.66)	0.014	1.05 (0.82 - 1.34)	0.716
Social function (<67 vs. ≥67)	1.42 (1.14 - 1.77)	0.002	1.30 (1.03 - 1.65)	0.030
Cognitive function (<67 vs. ≥67)	1.27 (1.02 – 1.58)	0.030	1.04 (0.82 – 1.33)	0.737
Abdominal/GI symptoms <13	1	0.004		0.470

>44 vs. <13	1.70 (1.23 - 2.35)	0.001	1.24 (0.86 - 1.80)	0.244
13-44 vs. <13	1.24 (0.93 – 1.66)	0.135	1.08 (0.79 - 1.48)	0.613

*Higher Physical, Role, Social, Cognitive and Global health scores indicate better health outcomes. Lower abdominal/GI score indicates better symptoms

**adjusted for neutrophil: lymphocyte≥5, platelets ($x10^9$/L, per 100 units), response to last line of therapy (PD/UK vs. CR/PR vs. SD), chemotherapy-free interval (months), ECOG performance status

Table 3. Univariable and multivariable analysis of baseline HRQL domains as predictors of overall survival (N=360)*

		Univariable analyses		**Multivariable analyses****	
QOL domain	**Median OS**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Physical function					
<58.33	10.5	2.24 (1.67 –	<0.001	1.61 (1.12 – 2.31)	0.011
≥58.33	21.1	2.99)			
Role function					
<66.67	14	1.91 (1.41 –	<0.001	1.45 (1.02 – 2.06)	0.041
≥66.67	25.8	2.61)			
Social function					
<67		1.74 (1.30 –	<0.001	1.47 (1.05 – 2.06)	0.026
≥67		2.33)			
Global Health Status					
<50	8.7	2.91 (2.16 –	<0.001	1.83 (1.28 – 2.62)	<0.001
≥50	22.8	3.93)			

Cognitive Function (<67 vs. ≥67)		1.47 (1.11 – 1.95)	0.007	1.12 (0.80 – 1.56)	0.504
Abdominal/GI symptom score					
<13	28.3		<0.001		0.161
13-44	17.3	1.67 (1.09 – 2.56)	0.017	1.50 (0.91 – 2.47)	0.108
>44	10.1	2.82 (1.80 – 4.41)	<0.001	1.69 (0.98 – 2.92)	0.058

*Higher Physical, Role, Social, Cognitive and Global health scores indicates better health outcomes. Lower Abdominal/GI scores indicate better symptoms.

**adjusted for presence of ascites, neutrophil: lymphocyte ≥5, platelets ($x10^9$/L, per 100 units), response to last line of therapy (PD/UK, CR, PR/SD), chemotherapy-free interval (months), log CA125, ECOG performance status, and BMI

Table 4. Univariable and multivariable analyses of baseline HRQL domains associated with stopping chemotherapy early (within 8 weeks, total N= 350)*

	Univariable analyses		Multivariable analyses**	
HRQL domain	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Global health status <50 vs. ≥50	2.59 (1.29-5.19)	0.007	1.46 (0.67- 3.19)	0.35
Physical function <58.33 vs. ≥58.33	2.70 (1.36 – 5.32)	0.004	1.64 (0.77 – 3.50)	0.20

*Higher Physical and Global health scores indicate better health outcomes. Lower abdominal/GI scores indicate better symptoms.

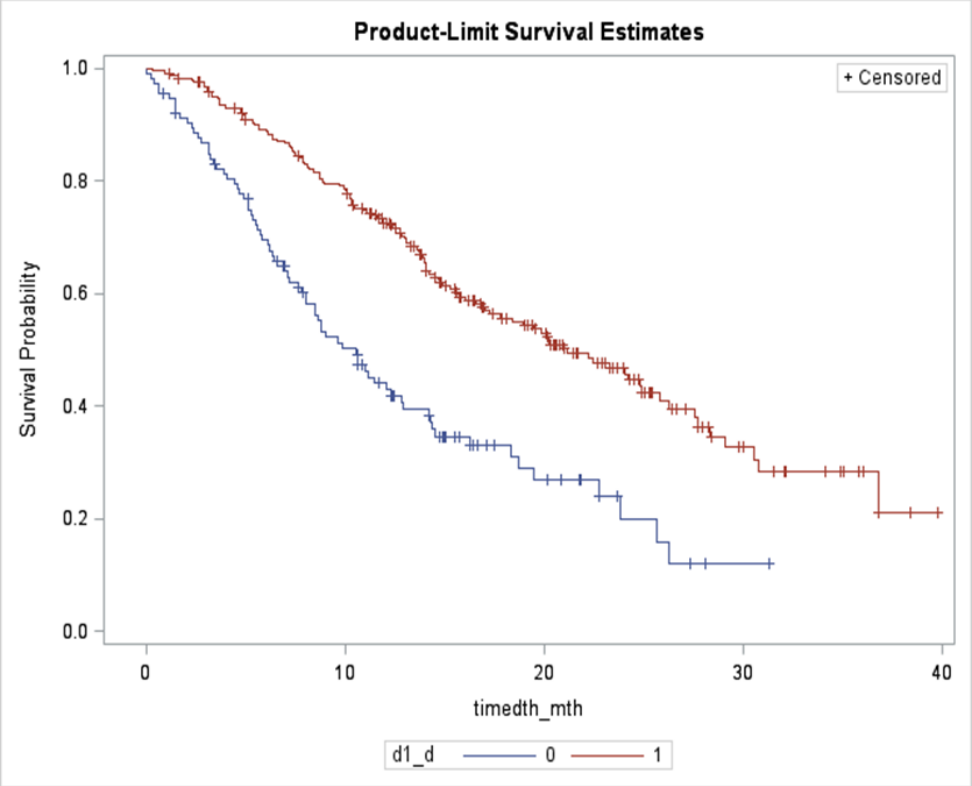
**adjusted for absolute neutrophil count≥7, neutrophil:lymphocyte≥5, ECOG performance status

Table 5. Nomogram points for each included factor and the relative weight compared to Abdominal/GI symptoms; Cox model parameter estimates

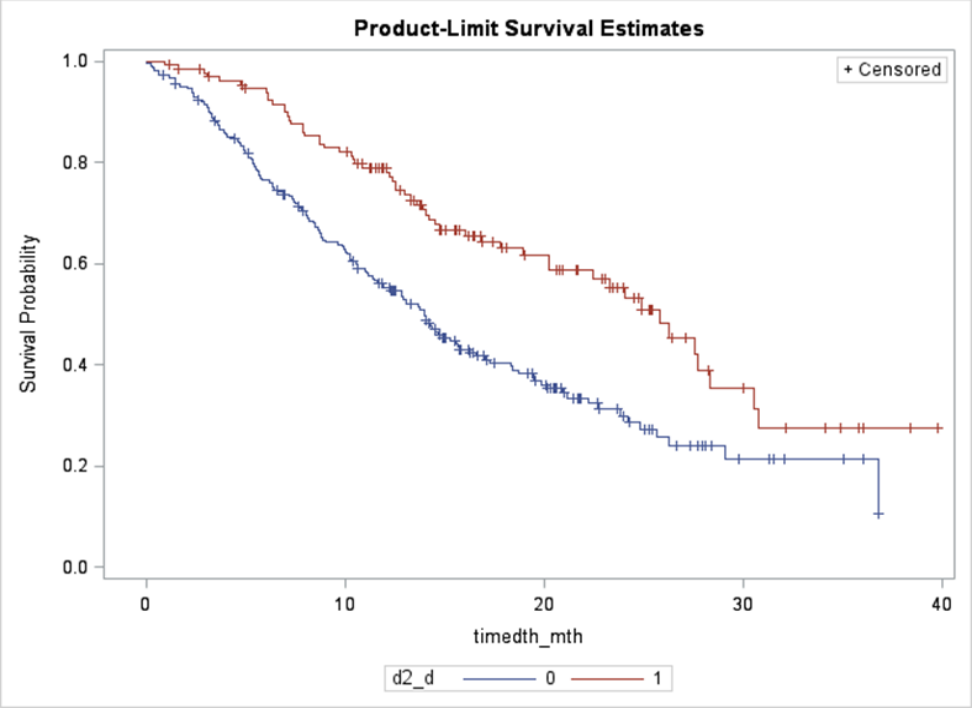
	Nomogram points			Cox PH Model estimates	
	With QoL	Relative weight	Without Qol	With QoL	Without QoL
Platelets (x10^9/L): >450 vs. <=450	62.5	1.7	67.5	0.410	0.441

Neutrophil/Lymp ratio: 5+ vs. <5	60	1.6	61	0.426	0.471
ECOG Performance status: 1 vs. 0	30	0.8	34	0.214	0.242
ECOG Performance status: 2+ vs. 0	100	2.7	100	0.683	0.692
Chemo-free interval: 12+ vs <12	52.5	1.4	53	-0.367	-0.403
Last response: CR/PR/SD vs PD/UK	54	1.4	52	-0.365	-0.397
Abdominal/GI: <50 vs 50+ 50+	37.5	1		-0.253	

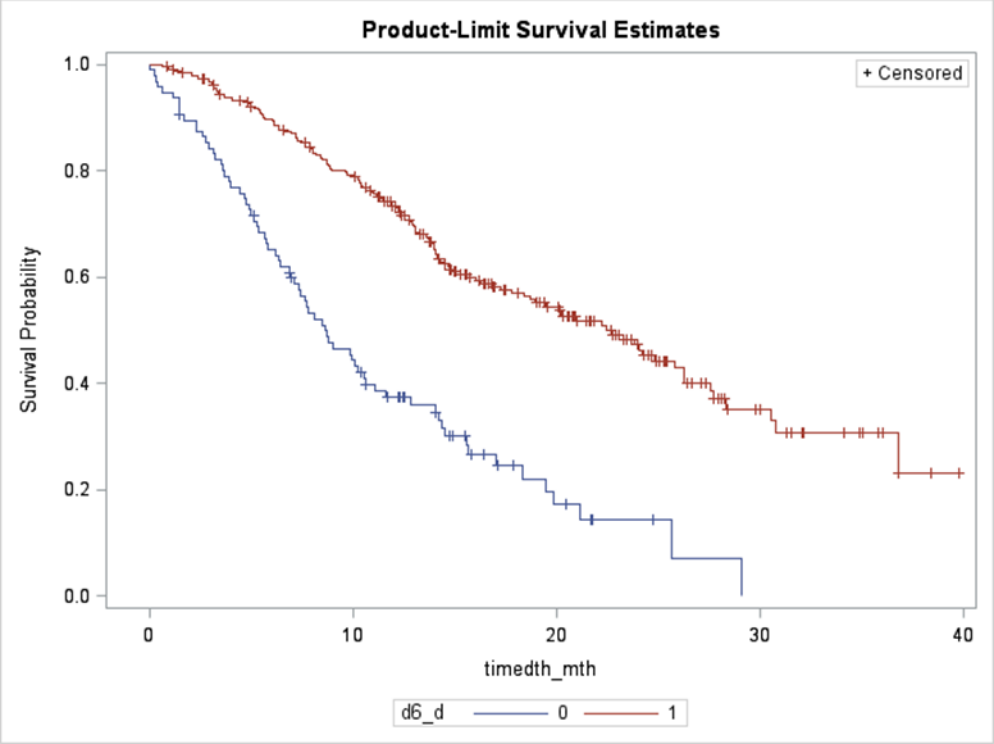
Figure 1. A. Kaplan-Meier curves for overall survival by HRQL domain



Physical Function

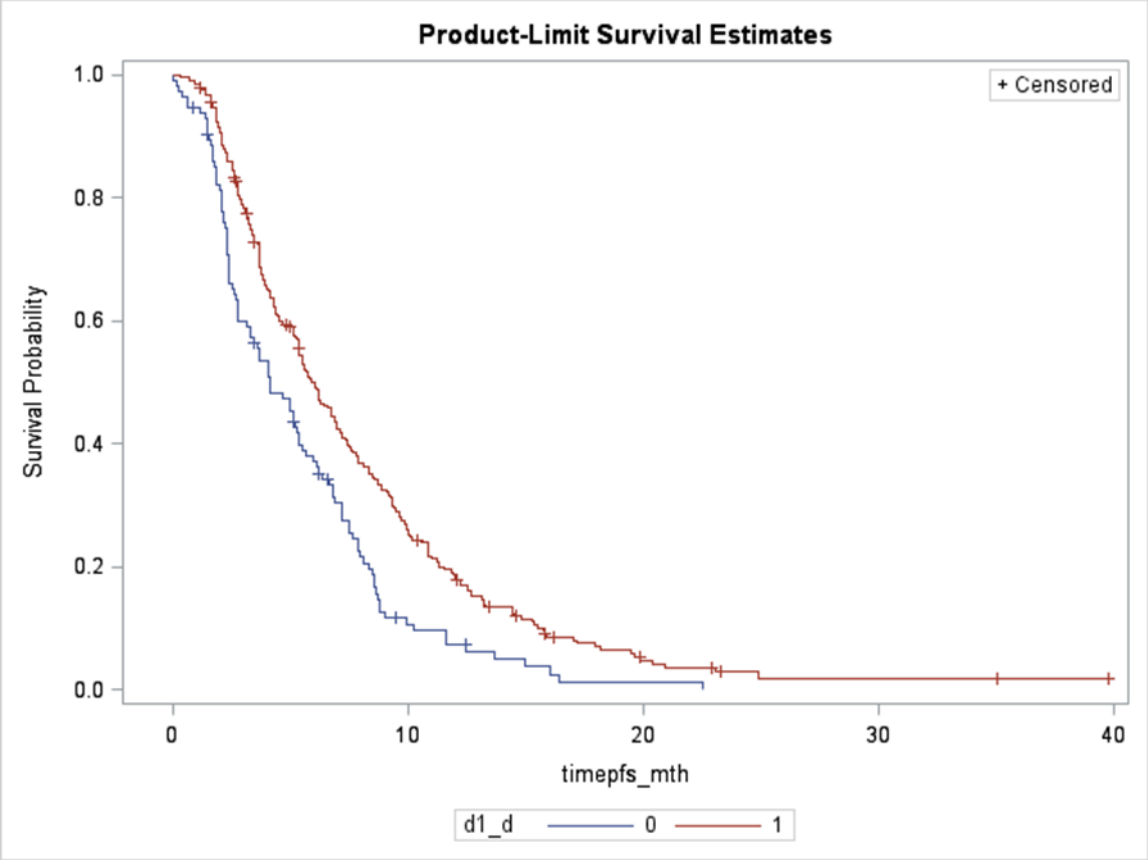


Role function

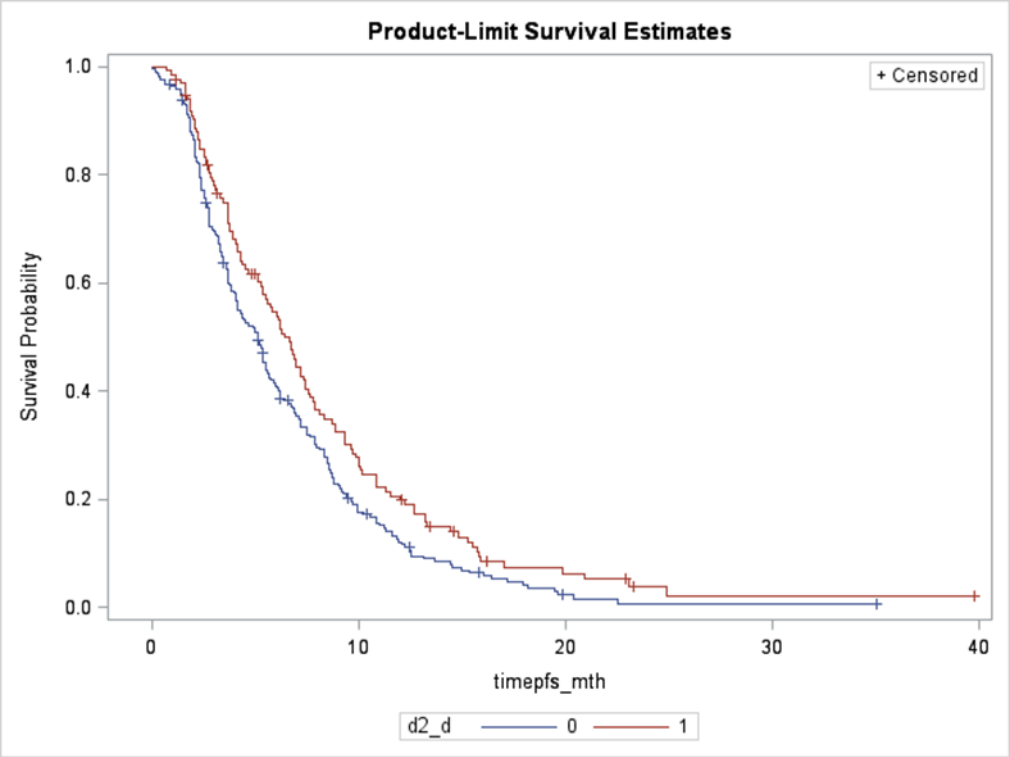


Global Health Status

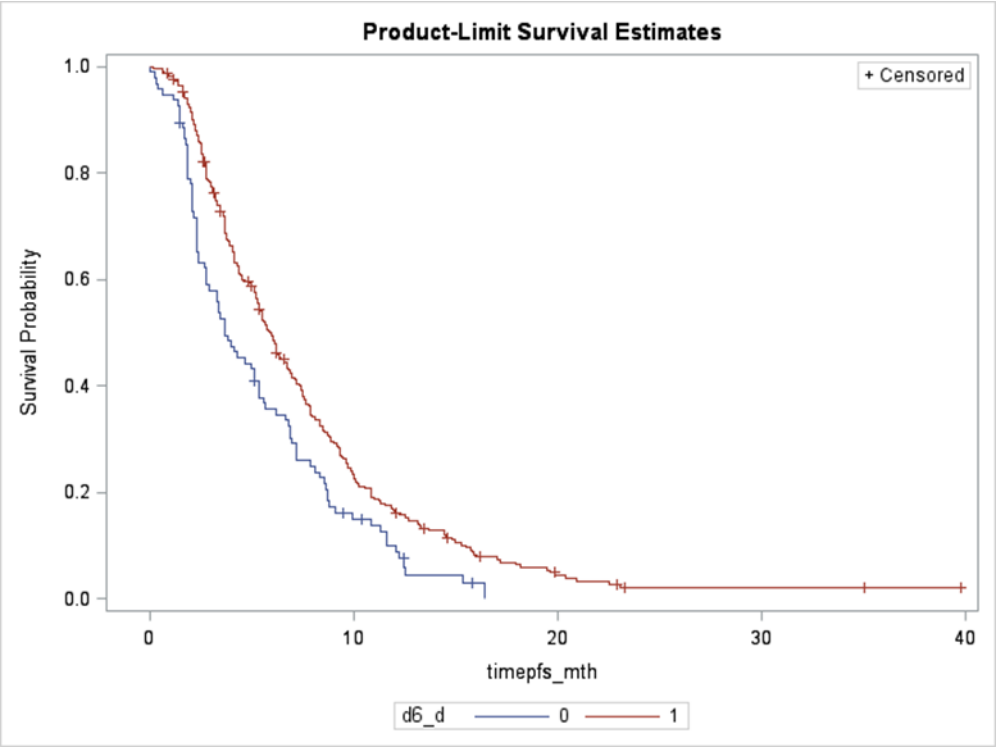
Figure 1. B. Kaplan-Meier curves for Progression-free survival by HRQL domain



Physical Function

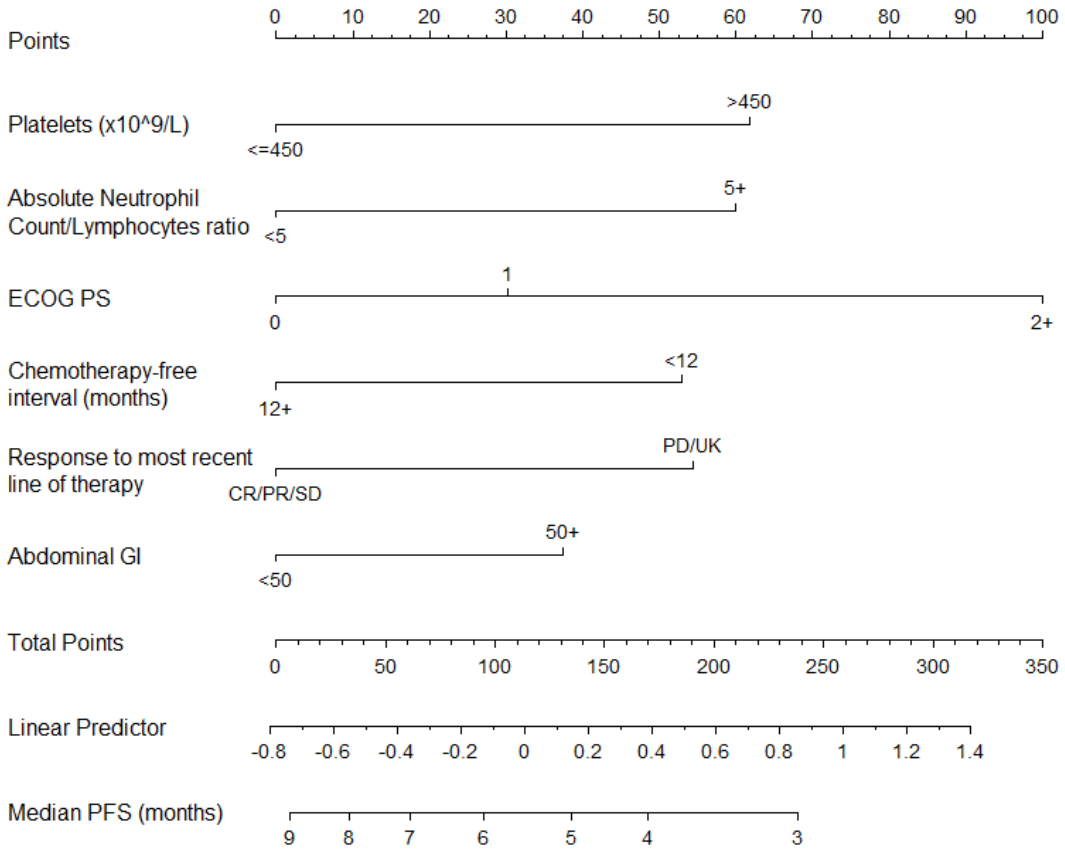


Role Function



Global Health Status

Figure 2. Nomogram for PFS in potentially platinum sensitive recurrent ovarian cancer about to start third or subsequent line of chemotherapy



Supplementary table 1. Univariable and multivariable analyses of baseline HRQL associated with stopping chemotherapy early (within 8 weeks) in those with good performance status (ECOG PS 0-1, total N=333)*

	Univariable analyses		Multivariable analyses**	
HRQL domain	Odds Ratio ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Global health status <50 vs. ≥50	2.53 (1.15 - 5.57)	0.021	1.85 (0.79 – 4.32)	0.158
Physical function <58.33 ≥58.33	2.90 (1.35 – 6.20)	0.006	2.32 (1.04 – 5.18)	0.040
Abdominal/GI symptom score <13 13-44 >44	 1 0.71 (0.25 – 2.00) 2.07 (0.74 - 5.77)	 0.043 0.515 0.164	 1 0.51 (0.17 – 1.49) 1.27 (0.43 – 3.76)	 0.119 0.217 0.668

*Higher Physical and Global health scores indicate better health outcomes. Lower Abdominal/GI scores indicate better symptoms.

**adjusted for Absolute neutrophil count (≥7) and chemotherapy-free interval.

Supplementary table 2. Women who stopped chemotherapy within 8 weeks or beyond 8 weeks according to ECOG PS

ECOG PS	Stopped chemo	

	within 8 weeks	beyond 8 weeks	Total
0	8	118	126
1	28	193	221
2	7	20	27
3	2	2	4
Total	45	333	378

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