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Quality of life is significantly associated with survival in women with advanced epithelial ovarian cancer: An ancillary data analysis of the NRG Oncology/Gynecologic Oncology Group (GOG-0218) study

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Abstract

Objective—Evaluate association between baseline quality of life (QOL) and changes in QOL measured by FACT-O TOI with progression-free disease (PFS) and overall survival (OS) in advanced epithelial ovarian cancer (EOC).

Methods—Patients enrolled in GOG-0218 with completed FACT-O TOI assessments at baseline and at least one follow-up assessment were eligible. Baseline FACT-O TOI scores were sorted by quartiles (Q1-4) and outcomes compared between Q1 and Q2-4 with log-rank statistic and multivariate Cox regression adjusting for age, stage, post-surgical residual disease size, and

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performance status (PS). Trends in FACT-O TOI scores from baseline to the latest follow-up assessment were evaluated for impact on intragroup (Q1 or Q2-4) outcome by log-rank analysis.

Results—Of 1152 eligible patients, 283 formed Q1 and 869 formed Q2-4. Mean baseline FACT-O TOI scores were 47.5 for Q1 vs. 74.7 for Q2-4 ($P < 0.001$). Q1 compared to Q2-4 had worse median OS (37.5 vs. 45.6 months, $P = 0.001$) and worse median PFS (12.5 vs. 13.1 months, $P = 0.096$). Q2-4 patients had decreased risks of disease progression (HR 0.974, 95% CI 0.953–0.995, $P = 0.018$), and death (HR 0.963, 95% CI 0.939–0.987, $P = 0.003$) for each five-point increase in baseline FACT-O TOI. Improving versus worsening trends in FACT-O TOI scores were associated with longer median PFS (Q1: 12.7 vs. 8.6 months, $P = 0.001$; Q2-4: 16.7 vs. 11.1 months, $P < 0.001$) and median OS (Q1: 40.8 vs. 16 months, $P < 0.001$; Q2-4: 54.4 vs. 33.6 months, $P < 0.001$).

Conclusions—Baseline FACT-O TOI scores were independently prognostic of PFS and OS while improving compared to worsening QOL was associated with significantly better PFS and OS in women with EOC.

Keywords

Ovarian cancer; Quality of life; FACT-O TOI; Survival; NRG Oncology/GOG

1. Introduction

For the approximately 22,000 patients projected to be diagnosed with ovarian cancer in 2015, the vast majority will have epithelial ovarian cancer (EOC) [1]. Maximal cytoreductive surgery and administration of adjuvant or neoadjuvant primary chemotherapy with a platinum and taxane combination regimen have proven to be the two most important factors influencing survival [2–6]. Apart from modifying the dose schedule [7] and route of administration of the platinum and taxane combination [8], there have been no new drugs alone or in combination with the platinum and taxane backbone that have resulted in improved overall survival (OS) [9]. Gynecologic Oncology Group trial 218, a trial evaluating the addition of bevacizumab both in combination with chemotherapy alone as well as a maintenance therapy following completion of primary chemotherapy and bevacizumab, noted a modest improvement in progression-free survival (PFS) of 3.8 months for patients receiving 21 total cycles of bevacizumab [10]. Having reached a temporary ceiling in OS using currently available surgical and chemotherapeutic practices, evaluating alternative clinical trial endpoints besides OS is crucial.

Alternative clinical trial endpoints such as progression-free survival (PFS) and quality of life (QoL) are increasingly being recognized for their importance [11]. Novel drug regimens may be preferred if they are better tolerated and prolong the disease free interval, while achieving equivalent OS benefits as the current standard of care. In searching for meaningful new endpoints, the patient reported outcomes (PROs) have emerged as relevant and patient-centered. QoL can be measured objectively with validated health related QoL (HRQoL) tools that capture patient's perceived functional, emotional, and physical well being status in conjunction with disease related symptoms and treatment adverse effects [12]. Considering

the emergence and relevance of QoL, a better understanding of the relationship between QoL and survival is needed.

Previous studies in EOC have demonstrated important associations between lower global QoL scores or specific QoL domain scores and decreased survival; however, the influence of patient performance status (PS) on QoL-attributed associations with survival in these studies may have been underestimated, leaving uncertainty about the true prognostic value of QoL scores on survival in EOC [13,14]. In addition, knowledge regarding the association between trends in QoL scores, obtained through serial HRQoL assessments, and survival is also undefined in EOC. In other tumor types, including prostate, lung and esophagogastric cancer, the existence of a significant association between QoL score trend and survival has been demonstrated [15–17]. A similar observation in EOC could alter clinical management and lead to greater emphasis on QoL to direct therapeutic decisions. Therefore, we sought to evaluate the relationship between baseline and serial QoL measurements and survival in EOC patients, measured using a validated HRQoL tool, the Functional Assessment of Cancer Therapy-Ovarian Trial Outcome Index (FACT-O TOI).

2. Methods

2.1. Patients

We performed a post hoc ancillary analysis of data from the randomized phase III Gynecologic Oncology Group 0218 trial (GOG-0218) to evaluate the independent prognostic ability of the (FACT-O TOI) HRQoL assessment tool for PFS and OS in advanced EOC patients. The cut-off date for survival calculations in this ancillary data analysis was April 2014. Patients enrolled on GOG-0218 had stage III optimal (<1 cm) or suboptimal (≥ 1 cm) cytoreduced or stage IV EOC, fallopian tube, or primary peritoneal cancer. Eligible patients were previously untreated, had a GOG performance status of ≤ 2, and met other pre-specified enrollment criteria in the study protocol [10]. In accordance with federal and institutional guidelines, all enrolled patients signed written informed consent for study participation to include receipt of study drug regimens, surveillance for treatment response and toxicity, and completion of HRQoL assessments at protocol-specified intervals.

2.2. Original study design

GOG-218 was a randomized three-arm, double-blinded, placebo-controlled, phase III clinical trial evaluating the survival impact of the addition of bevacizumab to adjuvant carboplatin and paclitaxel (cycles 2–6) with or without maintenance bevacizumab (cycles 7–22) compared to six cycles of carboplatin and paclitaxel alone. Disease progression, completion of therapy, unacceptable toxicity, and patient request were reasons for study termination [10]. Disease was assessed according to protocol before and throughout trial participation by radio-graphic, physical exam and serum tumor markers. Upon completion of the study, patients underwent systematic disease surveillance as outlined in the study protocol. Safety was monitored throughout using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [10].

2.3. Patient reported outcomes

HRQOL assessments in GOG-0218 were performed using the FACT-O questionnaire and reported in the trial outcome index (TOI) format [10, 18]. The TOI is a 26-item subset of the FACT-O questionnaire composed of the raw sum of the physical well-being subscale (7 questions), the functional well-being subscale (7 questions), and the ovarian cancer subscale (12 questions) [19]. Each question is scored on a scale of 0 (not at all) to 4 (very much) describing the frequency with which patients experience the symptom or condition described in the question [10,18]. The wording of some questions requires reverse coding of the scores to appropriately reflect the patient's symptom burden. The trial outcome index (TOI) describes the summation process of all the scores from each subsection into one composite score, termed the FACT-O TOI score. The maximum possible score on the TOI is 104 and higher scores reflect better QoL [10,18].

At six predefined time points patients completed FACT-O TOI questionnaires. One questionnaire was completed at baseline prior to receipt of any protocol chemotherapy. Four subsequent questionnaires were administered immediately preceding cycles 4, 7, 13, and 22 in order to accurately capturing QoL uninfluenced by the acute toxicities of the prior chemotherapy cycle. The final FACT-O TOI questionnaire was collected six months after completing protocol directed therapy [10]. The predefined objective for measuring QoL in GOG-0218 was to determine if the addition of bevacizumab reduced disease related symptoms quicker and more durably compared to the non-bevacizumab containing control regimen. The secondary objectives for measuring QoL were to evaluate the impact of bevacizumab on QoL. Results of these analyses have been previously reported [18].

2.4. Statistical design

All patients enrolled in GOG-0218 with completed baseline and at least one subsequent completed FACT-O TOI questionnaires were included in this analysis. Baseline FACT-O TOI scores were sorted and divided by quartile such that patients in the 1st quartile had the lowest scores, reflecting women with the worst QoL, and patients in the 4th quartile had the highest scores, representing those with the best QoL. Two cohorts were created for outcome comparison. Cohort 1 represented only patients with baseline FACT-O TOI scores in the 1st quartile (Q1) while cohort 2 consisted of all other baseline FACT-O TOI score quartiles combined (Q2-4). Cohort assignment by quartile was based on previously reported data showing that the association between QoL scores and survival in EOC is most apparent between the patients with scores in the lowest quartile compared to the highest quartile [14]. The χ^2 and Kruskal-Wallis tests were used to compare demographic variables between Q1 and Q2-4.

An inter-cohort (Q1 vs. Q2-4) survival comparison was then completed based on baseline FACT-O TOI scores alone. Log-rank survival analysis comparing OS and PFS between Q1 and Q2-4 was performed and the associated Kaplan-Meier plots were generated after censoring five years. A Cox proportional hazards model was fitted for both PFS and OS with adjustments for demographic variables that were found to be significantly ($p < 0.05$) different between Q1 and Q2-4 or variables with known independent prognostic significance. These variables were: age, performance status, stage of disease and residual

tumor size. Receipt of bevacizumab demonstrated no difference in survival for the cohorts, and thus it was not included in the model. Hazard ratio (HR) and 95% confidence intervals (CI) for variables listed in the Cox model correspond to five-point incremental increases in FACT-O TOI scores (continuous variables) and higher PS, disease stage, and patient age values (continuous variable).

The analysis also evaluated the association between survival and the FACT-O TOI score trend. To evaluate the survival impact of improving compared to worsening QoL as measured by the FACT-O TOI, an intra-cohort (within Q1 and within Q2-4) analysis was completed. In order to assess the association between serial QoL measurements and survival, the difference between the baseline FACT-O TOI score and the latest available subsequent FACT-O TOI score was calculated for patients within Q1 and within Q2-4. Within each cohort Log-rank survival analysis censored at five years with Kaplan-Meier plots evaluated the survival difference between Q1 patients with improving compared to worsening QoL, and Q2-4 patients with improving compared to worsening QoL.

3. Results

One-thousand-eight-hundred-seventy-three women enrolled in GOG-0218 between October 2005 and June 2009 were equally distributed among the three treatment arms. Of the study population 1152 women were included in this analysis by virtue of having completed both the baseline and at least one subsequent FACT-O TOI questionnaire. Table 1 demonstrates the clinicopathologic characteristics of qualifying patients according to cohort assignment by baseline FACT-O TOI score quartiles, Q1 or Q2-4. Patients in Q1 had significantly lower baseline FACT-O TOI scores and were more likely to have stage IV disease ($P = 0.041$), worse GOG performance status scores of 1 or 2 ($P < 0.001$), and ≥ 1 cm of residual disease ($P = 0.003$) compared to Q2-4 patients. There was no difference between cohorts in terms of study treatment arm allocation with both cohorts equally represented across the three protocol treatment arms ($P = 0.77$).

In the inter-cohort analysis of baseline FACT-O TOI scores, Q1 patients had worse survival outcomes compared to Q2-4 patients. The Kaplan-Meier curve in Fig. 1A demonstrates that Q1 patients had a median PFS of 12.5 compared to 13.1 months for Q2-4 patients ($P = 0.096$). Fig. 1B illustrates that Q1 patients had an 8.1 month shorter OS than Q2-4 patients (37.5 months vs. 45.6 months, $P = 0.0012$). The Cox multivariate regression analysis for PFS between Q1 and Q2-4 is displayed in Table 2. After adjusting for patient age, stage IV disease, the presence of ≥ 1 cm of residual disease, and PS of 1 and 2, a five-point increase in baseline FACT-O TOI score was independently prognostic of PFS (HR 0.974, 95% CI 0.953–0.995). Each year of advancing age (HR 1.01, 95% CI 1.004–1.02), stage IV disease (HR 1.12, 95% CI 1.03–1.39), and ≥ 1 cm of residual disease (HR 1.03, 95% CI 1.02–1.05) were also independently prognostic of PFS. Table 3 shows the Cox multivariate regression analysis for OS between Q1 and Q2-4. Each five-point increase in baseline FACT-O TOI score remained independently prognostic of OS (HR 0.963, 95% CI 0.939–0.987) after adjusting for patient age, stage IV disease, the presence of ≥ 1 cm of residual disease, and PS of 1 and 2. In the OS Cox model each year of advancing age (HR 1.017, 95% CI 1.01–1.03),

1 cm of residual disease (HR 1.02, 95% CI 1.002–1.04), and PS of 2 at study entry (HR 1.36, 95% CI 1.014–1.84) were also independently prognostic of OS.

The association between serial FACT-O TOI scores and survival outcomes for Q1 and Q2-4 is depicted in Fig. 2. Q1 patients with worsening QoL measurements had a PFS of 8.6 compared to 12.7 months ($P=0.001$) for Q1 patients with improved QoL (Fig. 2A). The OS for Q1 patients with worsening QoL measurements was 24.8 months shorter (16 vs. 40.8, $P<0.001$) than for those with improved QoL (Fig. 2B). For Q2-4 patients with worsening QoL during the study period PFS was 5.6 months shorter (11.1 vs. 16.7, $P<0.001$) compared to Q2-4 patients with improved QoL (Fig. 2C). Similarly, Q2-4 patients with worsening QoL scores had a 20.8 month shorter OS (33.6 vs. 54.4, $P<0.001$) compared to those with improving QoL (Fig. 2D).

4. Discussion

Our results demonstrate the independent prognostic value of HRQoL assessments in advanced EOC. Patients with baseline FACT-O TOI questionnaire scores in the lowest quartile have significantly worse OS than their peers with scores in the upper quartiles. A lower hazard of disease progression (HR 0.995, 95% CI 0.990–0.999) and death (HR 0.992, 95% CI 0.988–0.997) was associated with each five point increase in baseline FACT-O TOI score. Using the difference in mean baseline FACT-O TOI scores between Q1 (47.5) and Q2-4 (74.7), this equates to a 14% and 20% decreased risk of disease progression and death, respectively, for Q2-4 compared to Q1 patients.

In addition to the prognostic value of the baseline FACT-O TOI, we documented a prognostic relationship between change in QoL and subsequent survival. Among the high risk Q1 cohort, patients with improved QoL between the baseline and latest collected FACT-O TOI scores had significantly longer PFS and OS compared to other Q1 patients with worsened QoL. Among the Q2-4 cohort this relationship between improved QoL and significantly improved PFS and OS compared to worsened QoL persisted. Notably, Q1 patients with improving serial QoL measurements had superior PFS (12.7 vs. 11.1 months) and OS (40.8 vs. 33.6 months) compared to Q2-4 patients with worsening serial QoL measurements. While our results show that improving QoL is associated with longer survival, and worsening QoL is associated with shorter survival, there are potentially significant limitations to the applicability of these results. One such limitation rests in the variable duration used to assess change in QoL, which in this study was defined using the baseline FACT-O TOI score form and the latest available FACT-O TOI score form. In some cases this duration spanned up to six months after completing protocol directed therapy. Using a long time horizon, such as in this study, to define a change in QoL makes conclusions about the impact of changing QoL on survival, which may be possibly influenced by disease recurrence and in some cases treatment regimens for recurrent disease. Alternatively, using a shorter time frame to define change in QoL (such as baseline to a mid-therapy FACT-O TOI form) risks inaccuracies based on transient treatment-related side effects.

Another limitation that arises from the use of a variable final time point for determining change in QoL is that it limits the generalizability of our results to clinical practice. In other words, based on our results a provider remains unable to use a changing QoL data at a specific time point during or after treatment to direct patient care or counseling. Though we believe it is likely that changes in QoL detected by serial measurements are reflective of the underlying disease process rather than treatment tolerability or other factors, this cannot be definitively proven given the available data. If true, it implies that aggressive disease that is refractory to therapy correlates with deteriorating QoL and subsequently shorter survival. As a practical matter, one could treat the Q1-Q2 threshold as the cut point for pretreatment risk, and a 5-point worsening during the early treatment period as a worsening associated with increased risk of earlier progression or death, among those patients classified as scoring in the Q2-Q4 range. Patients scoring in the Q1 range who improve by 5 points, for example, could be considered as very low risk for early progression or death.

The relationship between baseline QoL and survival is well established in various cancer sites including EOC [20]. Wenzel et al. reported that mid-treatment FACT-O QOL scores in women with advanced and suboptimally debulked cancer were significantly associated with longer OS in an adjusted analysis that included age, measurable disease status, and stage [14]. Von Gruenigen and colleagues assessed QoL data from patients with advanced optimally debulked EOC who were enrolled in a randomized study comparing intravenous to intravenous/intraperitoneal chemotherapy (GOG-0172). Only the physical well-being FACT-G subscale demonstrated a significant association with survival in a multivariate analysis that adjusted for age, treatment, and the presence of gross disease [13]. Both of these important studies demonstrated that QoL measurements were prognostic of survival, however, neither of these studies adjusted for PS in the multivariate analysis. Wenzel et al. did report that patients who are fully active without restrictions (PS = 0) had a significantly improved survival compared to those patients who are capable of all self-care, but restricted by work activities (PS = 2) highlighting the possible influence of PS on clinical outcome. Establishing an independent association between global QoL score at baseline and survival requires adjusting for PS because most HRQoL assessment tools contain sub-scales related to physical and functional capability. Our analysis builds on prior evaluations in EOC and demonstrates that the FACT-O-TOI score (representing the physical and functional well being FACT-G sub-scales plus the FACT-O score) is independently prognostic of both PFS and OS after adjusting for PS, age, stage, and residual disease - all well accepted independent prognosticators of outcome in EOC [21].

Serial HRQoL measurements collected over the course of a patient's disease or treatment regimen can offer valuable insight into a patient's experience. When we analyzed the association between serial QoL measurements on OS and PFS the results demonstrated a clear association between worsening QoL and inferior survival. By completing this analysis within Q1 and Q2-4 independently we were able to show that after stratifying patients by risk according to baseline QoL score, worsening QoL scores were prognostic for survival in women with the worst baseline QoL scores as well as those with higher baseline scores. Improved serial QoL measurements were also associated with improved survival in patients with lung and esophagogastric cancers. Specifically in lung cancer, palliative chemotherapy leading to better physical and social wellbeing resulted in improved QoL scores, which were

associated with significantly improved survival. In an analysis of patients undergoing curative intent treatment for esophagogastric cancer, improved QoL scores attributed to restoration of physical function, diminution of fatigue and pain, and significantly improved survival. While our results coupled with similarly important associations between serial QoL scores and survival in other cancer sites are observational at this juncture, they support the need to better understand the true relationship between QoL and survival. Furthermore, prospective evaluation of multi-faceted interventions targeting improvement in QoL is warranted to determine if improved QoL can impact survival outcomes.

Given the importance of both baseline and serial QoL scores on survival in EOC, compliance with HRQoL measurement tools is crucial -both in clinical research and routine clinical care settings. While 100% compliance would be ideal, we had sufficient form completion to conduct baseline and early follow-up analyses. For use in ongoing care, however, it would be ideal to extend assessment well into the treatment period and beyond, so that the patient's own input can be factored into quality care. Initiatives like the Oncology Medical Home Model and the Oncology Care Model from the Center for Medicare and Medicaid Services, which include patient-reported data collection as a requirement, will further encourage the inclusion of HRQoL data into routine clinical practice. This may have a positive effect upon compliance, and results such as these provide the opportunity for meaningful use of the data collected in clinical practice. Further study can help refine how best to use the FACT-O TOI as a care quality management tool.

In conclusion, we demonstrate the independent prognostic value of the baseline QoL score after adjusting for important clinicopathologic variables including PS, while also revealing a potential novel association between serial QoL measurements and survival in EOC. Serially monitoring QoL during and after primary therapy could represent a new tool to monitor disease status and aid in therapeutic decisions while identifying targetable areas for implementation of QoL modifying interventions.

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Highlights

- Baseline QOL scores may predict survival in ovarian cancer patients.
- Identifying mechanisms to improve QOL for ovarian cancer patients may result in better outcomes.
- Serial improving QOL may predict improved patient outcomes.

Fig. 1.

Inter-cohort comparison of PFS (A) and OS (B) between Q1 and Q2-4. Median PFS was similar between cohorts, Q1 (12.5 months) and Q2-4 (13.1 months). Patients in the Q2-4 cohort lived 8.1 months longer than Q1 counterparts (median OS of 45.6 months vs. 37.5 months).

Fig. 2.

Association between quality of life trendon PFS (A) and OS (B) within Q1. Median PFS for worsening compared with improving quality of life was 8.6 compared to 12.7 months while median OS for worsening compared with improving quality of life was 16 compared to 40.8 months. In Q2-4 the median PFS (C) for worsening compared with improving quality of life was 11.1 compared to 16.7 months while median OS (D) for worsening compared with improving quality of life was 33.6 compared to 54.4 months.

Table 1

Patient characteristics (N = 1152).

Characteristic	Q1 (N = 283)		Q2-4 (N = 869)		P
	Mean (SD)		Mean (SD)		
Age	59.2 (10.4)		59.3 (10.5)		0.77
Baseline FACT-O TOI	47.5 (7.7)		74.7 (10.6)		<0.001
Characteristic	No.	%	No.	%	
Race					0.24
White	249	90	746	87	
Non-white	28	10	109	12	
Unknown	6	<1	14	<1	
Tumor histology					0.53
Serous	248	88	726	84	
Endometrioid	6	2	39	4	
Clear cell	4	1	21	2	
Mucinous	2	1	7	1	
Other	23	8	76	9	
Primary site					0.45
Ovary	231	82	729	84	
Fallopian tube	4	1	17	2	
Peritoneum	48	17	123	14	
Disease stage					0.041
III	197	70	658	76	
IV	86	30	211	24	
GOG Performance status					b0.001
0	95	34	504	58	
1	146	52	337	39	
2	42	15	28	3	
Residual disease					0.003
<1 cm	88	31	357	41	
1 cm	195	69	512	59	

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Characteristic	Q1 (N = 283)		Q2-4 (N = 869)		P
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Study arm					0.77
Control	91	32	293	34	
Bev initiation	100	35	287	33	
Bev throughout	92	33	289	33	

Table 2

Cox proportional hazards model for progression free survival.

Variable	Hazard ratio	Confidence interval	<i>P</i>
Increasing age	1.010	1.004–1.016	0.002
GOG PS 1	1.089	0.949–1.250	0.22
GOG PS 2	1.146	0.865–1.518	0.34
Baseline FACT-O TOI	0.974 ^a	0.953–0.995	0.018
Stage IV disease	1.198	1.032–1.390	0.018
1 cm Residual disease	1.031	1.015–1.047	<0.001

GOG; Gynecologic Oncology Group, PS; performance status, FACT-O TOI; functional assessment of cancer therapy-ovarian trial outcome index.

^aPer 5-point increase in FACT-O TOI.

Table 3

Cox proportional hazards model for overall survival.

Variable	Hazard ratio	Confidence interval	P
Increasing age	1.017	1.010–1.025	<0.001
GOG PS1	1.091	0.935–1.274	0.27
GOG PS2	1.364	1.014–1.835	0.04
Baseline FACT-O TOI	0.963 ^a	0.939–0.987	0.003
Stage IV disease	1.159	0.982–1.368	0.08
1 cm Residual disease	1.021	1.002–1.040	0.03

GOG; Gynecologic Oncology Group, PS; performance status, FACT-O TOI; functional assessment of cancer therapy-ovarian trial outcome index.

^aPer 5-point increase in FACT-O TOI.