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Quality of Life and Adverse Events: Prognostic Relationships in Long-Term Ovarian Cancer Survival

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Abstract

Background: There is a critical need to identify patient characteristics associated with long-term ovarian cancer survival. **Methods:** Quality of life (QOL), measured by the Functional Assessment of Cancer Therapy-Ovarian-Trial Outcome Index (FACT-O-TOI), including physical, functional, and ovarian-specific subscales, was compared between long-term survivors (LTS) (8+ years) and short-term survivors (STS) (<5 years) of GOG 218 at baseline; before cycles 4, 7, 13, 21; and 6 months post-treatment using linear and longitudinal mixed models adjusted for covariates. Adverse events (AEs) were compared between survivor groups at each assessment using generalized linear models. All *P* values are 2-sided. **Results:** QOL differed statistically significantly between STS (N = 1115) and LTS (N = 260) ($P < .001$). Baseline FACT-O-TOI and FACT-O-TOI change were independently associated with long-term survival (odds ratio = 1.05, 95% confidence interval = 1.03 to 1.06 and odds ratio = 1.06, 95% confidence interval = 1.05 to 1.07, respectively). A 7-point increase in baseline QOL was associated with a 38.0% increase in probability of LTS, and a 9-point increase in QOL change was associated with a 67.0% increase in odds for LTS. QOL decreased statistically significantly with increasing AE quartiles (cycle 4 quartiles: 0-5 vs 6-8 vs 9-11 vs ≥12 AEs, $P = .01$; cycle 21 quartiles: 0-2 vs 3 vs 4-5 vs ≥6 AEs, $P = .001$). Further, LTS reported statistically significantly better QOL compared with STS ($P = .03$ and $P = .01$, cycles 4 and 21, respectively), with similar findings across higher AE grades. **Conclusions:** Baseline and longitudinal QOL change scores distinguished LTS vs STS and are robust prognosticators for long-term survival. Results have trial design and supportive care implications, providing meaningful prognostic value in this understudied population.

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Advances in ovarian cancer treatments have improved 5-year survival rates for advanced-stage disease from 16% to 24% in the past 25 years (1). During the same period, only negligible improvements in long-term survival were observed (1). Therefore, there is a critical need to identify and understand differences between long and short-term ovarian cancer survivor characteristics to better stratify patients to conventional or experimental therapies, with the hope of statistically significantly improving survival rates overall.

Tumor biology (eg, cancer stage, grade, histology, cytology) and age at diagnosis have clear associations with overall survival (2). Considerable evidence has associated quality of life (QOL) at study initiation (3-11), as well as QOL changes over time (3), with statistically significant overall survival improvement. Although these relationships are not well understood, it is known that a cancer patient's responsiveness to cancer therapy may positively affect QOL by decreasing disease burden, thereby influencing survival. By extension, it is reasonable to expect that QOL is related to adverse events (AEs), because adherence to cancer treatment (12) and maintenance regimens (13–15) are clearly affected by experiencing AEs (16,17).

Examining both QOL and AEs across a clinical trial trajectory could assist in identifying the points in cancer treatment at which the probability for becoming a short-term survivor (STS) vs long-term survivor (LTS) can be detected and potentially addressed. Moreover, the extent to which the relationship between QOL and AEs might have prognostic value for long-term survival in this understudied population is unknown. Therefore, this study examines the relationship between QOL, measured by the Functional Assessment of Cancer Therapy-Ovarian-Trial Outcome Index (FACT-O-TOI) subscales examining physical, functional, and ovarian cancer-specific concerns, together with AEs, to identify characteristics associated with becoming a LTS of advanced ovarian cancer.

Methods

Patients

We used data from Gynecologic Oncology Group 218 (ClinicalTrials.gov numbers NCT02321735, NCT00262847), a phase III randomized clinical trial testing the efficacy of bevacizumab incorporated into standard frontline treatment of patients with stage III or stage IV ovarian epithelial, primary peritoneal, or fallopian tube cancer (18–20). 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 QOL assessments at protocol-specified intervals in accordance with institutional and federal guidelines.

Selected patients were classified into 3 groups based on the time interval between enrollment and death or last follow-up. LTS included those who survived 8 and more years from enrollment (n = 260); 73.1% were still alive at latest follow-up. STS included those who died within less than 5 years after enrollment (n = 1115). Patients who were alive at their last follow-up less than 5 years (n = 70, 5.9%) were excluded. Based on the natural history of the disease where median survival is known to be between 4 and 5 years, this group served as the reference population. Intermediate-term survivors (ITS) included those who died between 5 and 8 years from enrollment (n = 215). Patients still alive at last follow-up 5-8 years post enrollment (n = 42, 16.3%) who could belong to the LTS group were excluded from analyses for ITS.

Measures

QOL was measured using the FACT-O-TOI (21). The FACT-O-TOI is a 26-item summary score with a possible total of 112 points that captures the FACT-General QOL dimensions of Physical Well-Being (7 items), Functional Well-Being (7 items), and an Ovarian Cancer Subscale (12 items). The Functional Assessment of Cancer Therapy–Abdominal Discomfort (22) includes items on abdominal pain, swelling, and cramps. QOL and abdominal discomfort were measured at baseline; before cycles 4, 7, 13, 21; and 6 months after completing protocol-directed therapy. Patients completed questionnaires at scheduled assessment time points regardless of disease progression or if protocol-directed therapy was stopped secondary to toxicity.

AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3) (23) and reported until 30 days after the last study treatment had been administered. AEs were summarized for patients who received at least 1 cycle of bevacizumab or placebo (18). AE data collected during the QOL assessment time points are reported herein.

Statistical Analysis

Primary interest was in the association between QOL measurements and the probability of long-term survival in women newly diagnosed with advanced-stage ovarian cancer. These were quantified as the odds ratio (OR) of LTS (reference was STS) associated with a 1-unit increase in QOL or a 1-unit increase in the arithmetic change in QOL from baseline. QOL change across the treatment period was calculated as continuous change from baseline to the longest QOL follow-up data available from data collected at cycles 13 and 21 and post-treatment. Odds ratio estimates greater than 1.0 generally indicate better survival prognosis. All multivariable models included main-effect adjustment for age at diagnosis (continuous), stage (3 vs 4), grade (1 vs 2, 3), performance status (0, 1 vs 2), residual disease ($\leq$1 cm vs $>$1 cm), treatment (3 levels), and baseline QOL (continuous).

QOL was compared between LTS and STS at each assessment interval using multivariable linear models. Trends over time were compared using a longitudinal mixed model adjusted for covariates. Odds ratios for LTS (reference was STS) associated with QOL at each timepoint were estimated using the timepoint-specific multivariable logistic regression model, with a main effect for Trial Outcome Index at the measured time point. Odds ratio estimates for a 7-point increase in QOL are also provided. To further elucidate the association between QOL and survival for the ITS group in addition to LTS and STS, adjusted ORs associated with QOL and QOL change for LTS (reference was STS) and ITS (reference was STS) associated with a 1-unit QOL increase in the furthest assessed timepoint were estimated using a multivariable polychotomous regression model. Additional analyses were conducted to examine differences between LTS and STS in baseline QOL and QOL change scores stratified by treatment response category, classified as responders, nonresponders, and those nonmeasurable. Treatment response and completed cycles of treatment were added to the multivariable model to investigate the prognostic value of QOL and QOL change independent of treatment response.

Table 1. Demographic and patient characteristics for short- and long-term survivors

Characteristics	Survive ≤5 y (n = 1115)	Survive 8+ y (n = 260)	P[a]
Mean age (SE), y [No.]	60.43 (0.33) [1003]	58.01 (0.68) [244]	.001
Race or ethnicity, No. (%)			
American Indian	4 (0.4)	1 (0.4)	.07
Asian	58 (5.2)	23 (8.8)	—
Black	50 (4.5)	8 (3.1)	—
White non-Hispanic	949 (85.1)	211 (81.2)	—
Hispanic	37 (3.3)	14 (5.4)	—
Unknown	17 (1.5)	3 (1.2)	—
Treatment, No. (%)			
Chemotherapy	387 (34.7)	91 (35.0)	.18
Chemotherapy + bevacizumab	376 (33.7)	74 (28.5)	—
Chemotherapy + bevacizumab + bevacizumab	352 (31.6)	95 (36.5)	—
Stage, No. (%)			
III	775 (69.5)	213 (81.9)	<.001
IV	340 (30.5)	47 (18.1)	—
Grade, No. (%)			
1	31 (3.1)	17 (7.01)	.02
2	125 (12.5)	30 (12.3)	—
3	847 (84.4)	197 (80.7)	—
Performance status, No. (%)			
0	477 (47.0)	90 (54.2)	<.001
1	458 (45.2)	69 (41.6)	—
2	79 (7.8)	7 (4.2)	—
Residual disease, No. (%)			
≤1 cm	479 (43.0)	144 (55.4)	<.001
>1 cm	636 (57.0)	116 (44.6)	—
FACT-O-TOI[b] at baseline, mean (SE) [No.]	66.26 (0.49) [968]	68.89 (0.99) [238]	.02
FACT-O-Physical Well-Being[b] at baseline, mean (SE) [No.]	19.83 (0.17) [967]	21.04 (0.36) [238]	.002
FACT-O-Functional Well-Being[b] at baseline, mean (SE) [No.]	14.30 (0.19) [968]	14.94 (0.40) [238]	.15
FACT-O-Additional Concerns[b] at baseline, mean (SE) [No.]	32.15 (0.20) [968]	32.93 (0.40) [238]	.08
Abdominal Discomfort[c] at baseline, mean (SE) [No.]	11.48 (0.12) [968]	12.32 (0.24) [238]	.002

[a]Differences for categorical variables are tested with a 2-sided Pearson χ^2 test; difference in mean age is tested using a 2-sided *t* test.

[b] Means for FACT-O-TOI and subdomains are adjusted for age, stage, grade, performance status, residual disease, and treatment. Higher scores reflect better quality of life. Differences are tested with a 2-sided F test.

[c]Mean scores are adjusted for age, stage, grade, performance status, residual disease, and treatment. Higher scores reflect less abdominal discomfort. Differences are tested with a 2-sided F test.

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Mean number of all AEs and grade 2 or higher AEs were compared across the treatment period using generalized linear models. Differences between LTS and STS in QOL across increasing quartiles of all AEs and grade 2 or higher AEs were investigated using multivariable linear models.

Missing data are assumed to be missing at random. P values less than .05 were deemed statistically significant, with no multiple testing adjustment. All P values are 2-sided.

Results

Baseline Characteristics

Analyses comparing LTS and STS included 1375 patients. Of those, 260 were identified as LTS (8+ years), and 1115 were identified as STS (<5 years). STS and LTS did not differ statistically significantly with respect to age, ethnicity, or treatment (Table 1). However, LTS were less likely to have stage IV disease (18.1% vs 30.5%, $P < .001$), high-grade disease (93.0% vs 96.9% grade 2 or 3, $P = .02$), poor performance status (4.2% vs 7.8%, $P < .001$), and residual disease greater than 1 cm (44.6% vs 57.0%, $P < .001$).

Relationship Between QOL and Long-Term Survival

After adjusting for covariates, we identified a statistically significant difference in QOL over time between the STS and LTS ($P < .001$; Figure 1) and demonstrated a statistically significantly increased probability of being an LTS (Table 2). The difference between the groups increased over time, with the exception of cycle 7 (Figure 1; Table 2). Further, a 7-point change (0.5 SD) in the FACT-O-TOI, which is considered clinically meaningful (24), was established first before cycle 4 as being associated with a 9.5% increase in the likelihood of long-term survival, expanding to a 44.9% increased likelihood of long-term survival at 6 months posttreatment (Table 2).

In polychotomous logistic regression adjusting for covariates, both baseline FACT-O-TOI and change in FACT-O-TOI were statistically significantly and independently associated with an increased probability of being an LTS relative to STS (OR = 1.05, 95% confidence interval [CI] = 1.03 to 1.06 and OR = 1.06, 95% CI = 1.05 to 1.07, respectively; Table 3). Moreover, a clinically meaningful change of 0.5 SD in baseline QOL (7 points) was associated with a 38.0% increase in probability of being an LTS, and a change of 0.5 SD in QOL change (9 points) was associated with a 67.0% increase in odds for long-term survival. When comparing factors associated with survival for the

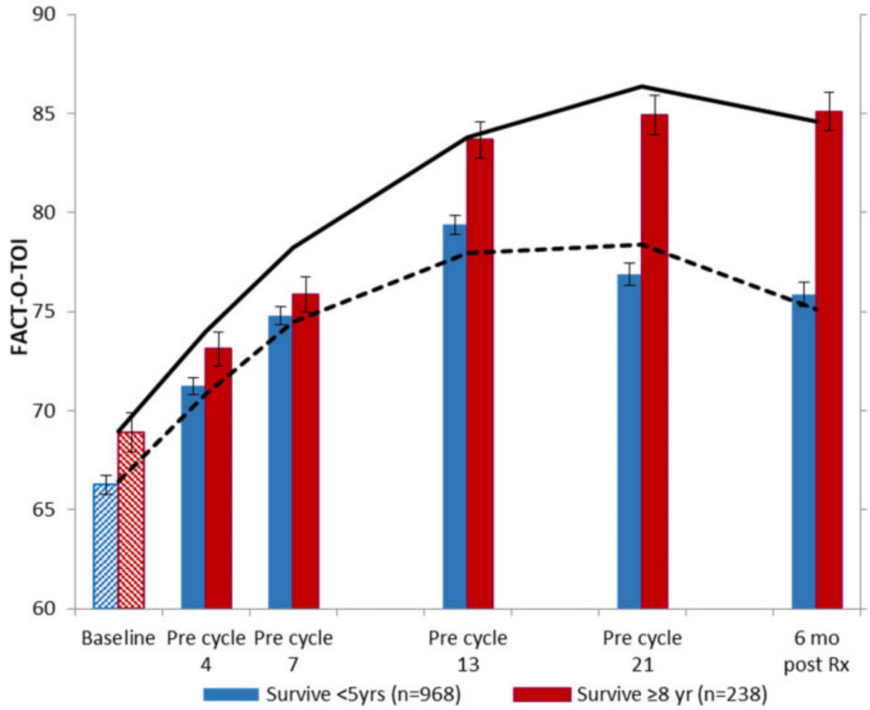

Figure 1. Analysis compares Functional Assessment of Cancer Therapy–Ovary Trial Outcome Index (FACT-O-TOI) between short-term survivors (STS) and long-term survivors (LTS) at each assessment interval using mixed hierarchical regression, adjusting for age, stage, grade, performance status, residual disease, treatment, and baseline FACT-O-TOI for cycle 4 and later. **Solid line** represents FACT-O-TOI in LTS from mixed model; **dotted line** represents FACT-O-TOI in STS from mixed model. This analysis shows statistically significant differences between survivor groups at baseline that continue to grow over time. Error bars represent ±1 standard error. Rx = treatment.

Table 2. Odds ratios for prediction of long-term survival (dependent variable) associated with FACT-O-TOI at different treatment time points (adjusted for age, stage, grade, performance status, residual disease, treatment, and baseline FACT-O-TOI)

Dependent variable	STS, No.	LTS, No.	OR (95% CI)	SE	*P*[a]	Increase in adjusted OR for LTS with 7 pt increase in FACT-O-TOI
TOI at pre-cycle 4	863	225	1.01 (1.00 to 1.03)	0.01	.04	1.10
TOI at pre-cycle 7	832	219	1.01 (1.00 to 1.02)	0.01	.27	1.05
TOI at pre-cycle 13	729	215	1.03 (1.02 to 1.04)	0.01	<.001	1.22
TOI at pre-cycle 21	614	215	1.05 (1.04 to 1.07)	0.01	<.001	1.40
TOI at 6 mo post treatment	510	209	1.06 (1.04 to 1.07)	0.01	<.001	1.45

[a]Data tested using 2-sided z-test. CI = confidence interval; FACT-O-TOI = Functional Assessment of Cancer Therapy–Ovary Trial Outcome Index; LTS = long-term survivor; OR = odds ratio; SE = standard error; STS = short-term survivor; TOI = Trial Outcome Index.

Table 3. Odds ratios for survival of 5-8 years and 8 years and more, relative to less than 5 years associated with FACT-O-TOI and change in FACT-O-TOI adjusted for patient covariates[a]

Parameter	Estimate	SE	*P*[b]	OR[a] (95% CI)
Survive 5-8 y vs <5 y (ref)				
FACT-O-TOI baseline	0.036	0.007	<.001	1.04 (1.02 to 1.05)
Change in FACT-O-TOI[c]	0.039	0.006	<.001	1.04 (1.03 to 1.05)
Survive ≥8 y vs <5 y (ref)				
FACT-O-TOI baseline	0.046	0.007	<.001	1.05 (1.03 to 1.06)
Change in FACT-O-TOI[d]	0.057	0.006	<.001	1.06 (1.05 to 1.07)

[a]Reference: survive less than 5 years: 827; survive 5-8 years: 227; survive 8 years and more: 233. Deleted for missing data: 415. CI = confidence interval; FACT-O-TOI = Functional Assessment of Cancer Therapy–Ovary Trial Outcome Index; OR = odds ratio; QOL = quality of life; ref = reference; SE = standard error.
[b]Data tested using 2-sided z-test.
[c]Odds ratios adjusted for age, stage, grade, performance status, residual disease, and treatment.
[d]Change measured from baseline to longest QOL follow-up of cycle 13, cycle 21, or post-treatment.

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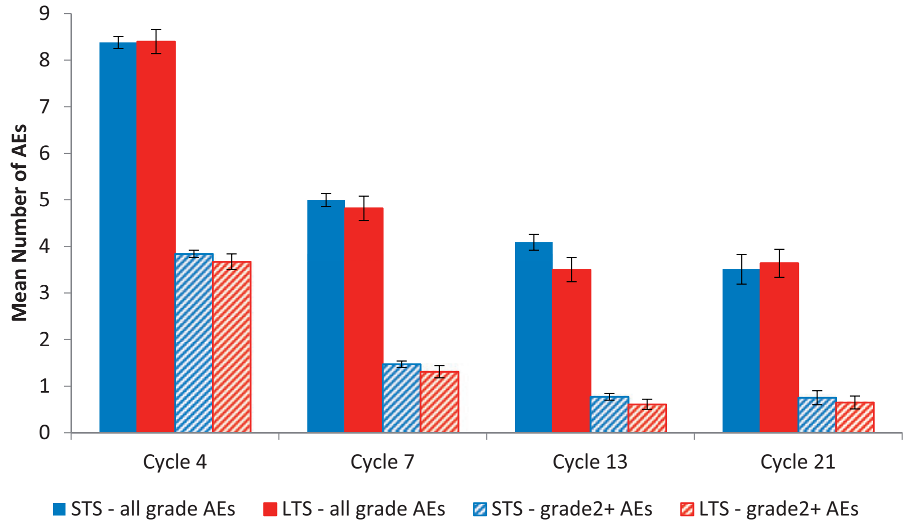

Figure 2. Mean number of adverse events (AEs) by survivorship across treatment period. Total number of AEs does not differ statistically significantly between long-term survivors (LTS) and short-term survivors (STS) at cycle 4 ($P = .95$), cycle 7 ($P = .53$), cycle 13 ($P = .06$), or cycle 21 ($P = .76$). Number of grade 2 or higher AEs does not differ statistically significantly between LTS and STS at cycle 4 ($P = .38$), cycle 7 ($P = .26$), cycle 13 ($P = .18$), or cycle 21 ($P = .65$). Data are tested using a 2-sided *t* test. Error bars represent ±1 standard error.

intermediate group surviving 5-8 years relative to STS, baseline FACT-O-TOI and change in FACT-O-TOI were again statistically significantly associated with survival, but at a level intermediate between the STS and LTS (OR = 1.04, 95% CI = 1.02 to 1.05 and OR = 1.04, 95% CI = 1.03 to 1.05, respectively).

We further examined the associations of each subscale of the FACT-O-TOI with LTS. When the subscales of Physical Well-Being, Functional Well-Being, and Additional Concerns were included as separate variables in the logistic regression model, change in each subscale contributed statistically significantly and independently to the likelihood of being an LTS. Odds ratios for long-term survival associated with change in Physical Well-Being, Functional Well-Being, and Additional Concerns were, respectively, 1.06 (95% CI = 1.03 to 1.11), 1.06 (95% CI = 1.03 to 1.09), and 1.05 (95% CI = 1.02 to 1.08) after adjusting for baseline QOL and patient covariates (data not shown).

We examined the differences in baseline QOL and QOL change stratified by treatment response, classified as nonresponder, responder (partial or complete), and nonmeasurable disease. Baseline QOL scores did not differ statistically significantly by response category adjusted for long-term survival status, with baseline Trial Outcome Index values of 68.2, 68.0, and 68.7 for nonresponders, responders, and nonmeasurables, respectively ($P = .87$). QOL change scores of the nonmeasurable patients (N = 398) were similar to the responders (N = 550) with a mean QOL change of 11.4 and 11.1, respectively, whereas the nonresponders (N = 185) had a statistically significantly smaller QOL change (mean = 4.6; $P = .03$). Further, when comparing prognostic factors of LTS compared with STS, QOL change was greater for LTS than STS for each treatment response category ($P < .0005$), with no statistically significant variability by response status (ie, no interaction, $P = .70$). In multivariable analysis, after adjustment for completed cycles of treatment and response to treatment, both baseline QOL and QOL change retained statistically significant prognostic value for long-term survival ($P < .001$ for each) with minimal change (<0.4%) in the respective adjusted ORs for long-term survival.

Relationship Between QOL, AEs, and Long-Term Survival

AEs were most frequent at cycle 4, decreasing across the remainder of the treatment period. When AEs were compared between survivor groups, there were no statistically significant differences between the 2 survivor groups with respect to number of all AEs at cycles 4, 7, 13, or 21 after adjusting for baseline characteristics (Figure 2). In early vs later treatment cycle comparisons, QOL decreased statistically significantly with increasing quartiles of AEs ($P = .01$ at cycle 4 and $P = .001$ at cycle 21) (Figure 3), and LTS had statistically significantly better QOL compared with STS for each quartile of AEs ($P = .03$ and $P = .01$ for cycles 4 and 21, respectively). Similarly, statistically significant QOL decreases were observed across quartiles representing increasing levels of grade 2 or higher AEs ($P < .001$ at cycle 4, $P = .02$ at cycle 21) with higher levels of QOL in LTS vs STS at each level of AEs (Figure 4). Associations between QOL and AEs were similar at cycles 7 and 13, with statistically significant decreases in QOL across AE quartiles but nonstatistically significantly higher QOL in LTS.

We further examined abdominal discomfort, all AEs, and grade 2 or higher AEs at each time point in separate logistic regression models to determine if these measures were statistically significantly related to long-term survival. After adjusting for patient baseline covariates, baseline QOL, and QOL change, abdominal discomfort measured at cycle 4, 7, 13, or 21 was not statistically significantly associated with long-term survival. Further, after adjusting for patient covariates and QOL in multivariable logistic regression models, all AEs and grade 2 or higher AEs measured at any time point were not statistically significantly associated with the probability of long-term survival.

Finally, to potentially provide an additional explanation for short- vs long-term survival, the relationship between AEs, treatment discontinuation, and survival was examined. As reported (18), 66% of patients discontinued treatment prematurely, with progressive disease cited as the most common

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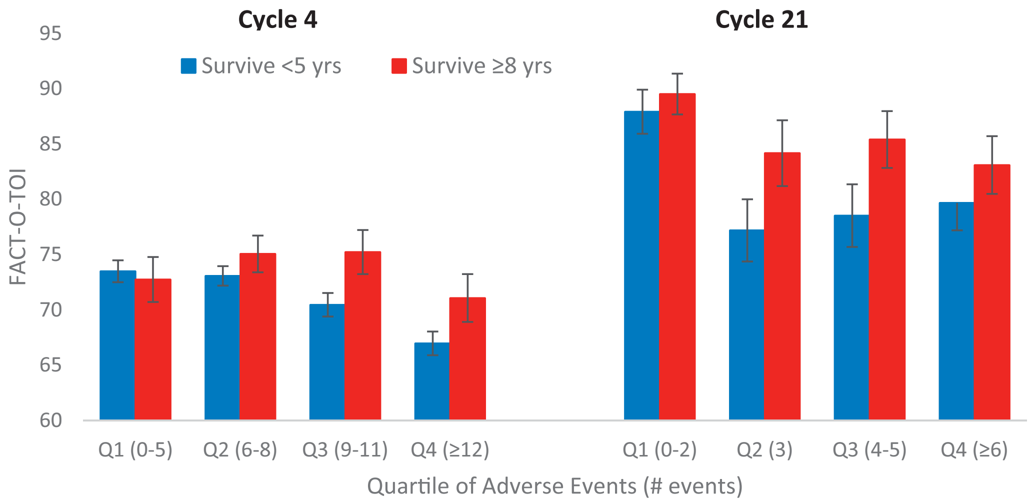

Figure 3. Functional Assessment of Cancer Therapy–Ovary Trial Outcome Index (FACT-O-TOI) by survivorship and quartiles of all adverse events (AEs). Long-term survivors have higher FACT-O-TOI at cycle 4 ($P = .03$) and cycle 21 ($P = .01$). FACT-O-TOI decreases with increasing AEs at cycle 4 ($P = .01$) and cycle 21 ($P = .001$). Data are tested using a 2-sided F test. Error bars represent ±1 standard error. Q = quartile.

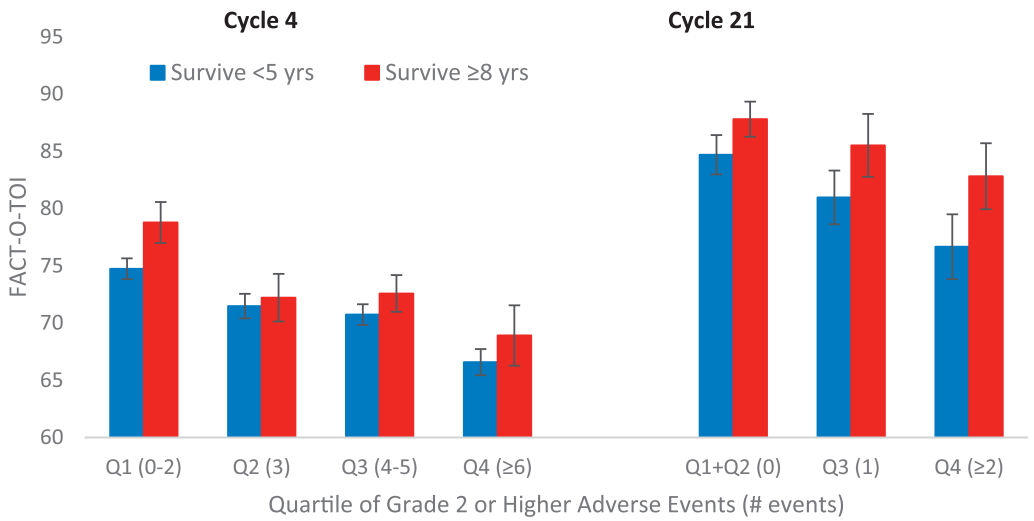

Figure 4. Functional Assessment of Cancer Therapy–Ovary Trial Outcome Index (FACT-O-TOI) by survivorship and quartiles of grade 2 or higher adverse events (AEs). Long-term survivors have higher FACT-O-TOI at cycle 4 ($P = .05$) and cycle 21 ($P = .02$). FACT-O-TOI decreases with increasing grade 2 or higher AEs at cycle 4 ($P < .001$) and cycle 21 ($P = .02$). Data are tested using a 2-sided F test. Error bars represent ±1 standard error. Q = quartile.

reason for discontinuation (39% of patients), whereas only 15% discontinued treatment due to AEs. Among those who discontinued due to AEs, no statistically significant differences between LTS and STS in total number of AEs, or grade 2 or higher AEs at cycle 4, cycle 7, or cycle 13 were observed (insufficient data to test at cycle 21). When patients were stratified by quartile of treatment cycles received, mean total AEs, or grade 2+ AEs at cycle 4, 7, 13, or 21, they were not statistically significantly different between LTS and STS. However, after adjusting for cycles of treatment completed, a difference between LTS and STS in QOL and QOL change persisted.

Discussion

In this phase III advanced ovarian cancer clinical trial of more than 1500 patients, we compared differences between STS (<5 years) and LTS (8+ years) on QOL and AE variables. We found that both baseline QOL and longitudinal change in QOL were statistically significantly and independently associated with increased probabilities of being an LTS, reinforcing the prognostic value of both baseline and change scores. Further, the increasing probability of being an LTS, illustrated through the 0.5-SD change in scores, demonstrates a clinically meaningful magnitude of change considered relevant in determining effect sizes for patient-reported outcomes (PROs) (24) and is thought to be large enough to have implications for a patient's treatment or care (25,26).

With respect to the LTS population, the widening QOL gap is readily apparent as patients are both undergoing (eg, cycle 4) and completing (eg, cycle 21) treatment, with increasing odds of becoming an LTS across the treatment cycles. It is therefore noteworthy that longitudinal change, as measured by the FACT-O-TOI, is a meaningful prognosticator of long-term survival, likely capturing both disease effects and response to treatment. With respect to treatment response, this becomes evident when linking QOL to the treatment response categories as responders, nonmeasurables, or nonresponders. QOL did reflect treatment response and could serve as a marker of clinical benefit. However, independent of response to treatment, there remains a statistically significant difference between LTS and STS in QOL change that is not attributable to the treatment. Therefore, we interpret these data as indications that QOL change over the treatment period is statistically significantly associated with treatment response categories but also stands as an independently statistically significant and robust prognosticator for long- vs short-term survival. These LTS vs STS score gaps are particularly notable because each assessment time point introduces a meaningful opportunity to examine patient-reported deteriorations that might be amenable to supportive care interventions earlier in the treatment trajectory.

With recognition that the number or severity of AEs might influence QOL, we examined that relationship and its association with short- vs long-term survival. This question has important implications for treatment direction, because it is often the case that toxicities could result in treatment delays, dose reductions, or treatment discontinuation, which might in turn affect progression-free survival or overall survival. In this study, where 15% of patients discontinued treatment due to AEs, there were no statistically significant differences between LTS and STS in either mean total AEs or grade 2+ AEs. However, experiencing more or worse AEs was associated with decreased QOL, which is not a surprising finding. It is interesting, however, that the QOL of LTS was consistently better than that of STS for every quartile of both number or increasing grade of AEs, suggesting a certain resilience or tolerance among the LTS, which is being captured specifically through QOL measurement. In short, QOL measurement did differentiate between the STS and LTS groups, whereas the AEs recorded as mean total or 2+ grade did not. Some of this difference, at least related to symptom reports, may be attributed to discrepancies between patient-reported and physician-reported measures of toxicity to the extent they are related to QOL, specifically recognizing that patients are more likely to report more serious toxicities (27) and more AEs across symptoms compared with clinicians (28). Our results provide additional support to recommendations that incorporating PROs into clinical practice can be complementary to clinician-reported data (29), which could improve patients' health-related QOL, increase treatment adherence (30), and may positively affect overall survival (28).

There is an important interplay between PROs and AEs that deserves further attention, because novel analytic methods accounting for the burden of multiple toxicities, such as those analyzed through a toxicity index (31), may provide a more complete description of the treatment experience. This consideration may be particularly valuable in the recurrent ovarian cancer setting, where the impact of cumulative toxicity associated with multiple lines of therapy on QOL must be weighed against potential impact on progression-free survival (32).

This study supports early work in oncology clinical trials (33,34) as well as recent work (4,9,35) hypothesizing that PRO data are statistically significantly associated with survival because they inform prognostically relevant decreases in well-being earlier than other measures (34). Similarly, patient-reported symptoms and toxicities have been mapped to objective responses and functional status changes during chemotherapy (36), and calculated patient-reported symptoms and physical well-being change scores have been linked to best and worst responses to treatment as well as survival. Taken together, PRO data have been linked to toxicity development, treatment response, and treatment outcomes, including ovarian cancer outcomes (3). This study not only supports this prior literature, but also contributes to this body of work by emphasizing the importance of QOL independently serving as a robust prognostic indicator specifically for long-term ovarian cancer survival, particularly related to QOL change during treatment. This adds value that is not explained by patient covariates, cancer treatment, or treatment adherence. Therefore, real-time QOL score changes could be monitored to identify thresholds for treatment reevaluation and/or supportive care strategies.

By examining QOL across the treatment trajectory in a large, well-controlled clinical trial together with AE development, we identified additional characteristics associated with becoming an LTS of advanced ovarian cancer. We propose that these results underscore the opportunities suggested by many that clinical trial precision can be enhanced by using QOL as a stratification factor (34,35) as well as guiding ovarian cancer care delivery in a meaningful, measurable way to improve QOL, symptom management, and perhaps improve on the numbers of women becoming LTS.

We acknowledge certain limitations of this study. First, the importance of biobehavioral factors, such as social and emotional determinants of well-being, should not be overlooked because they relate to QOL, survival, and long-term survivorship. Psychosocial dimensions assist in characterizing LTS (37), including the importance of high social attachment (38), with strong implications for future directions. Secondly, the low proportion of minorities in this clinical trial does not reflect the distribution of ovarian cancer by race. Because the population in this study was relatively homogeneous, the ability to detect differences that may be present in a more diverse or broader population is limited (39,40). The social determinants of health, including race, ethnicity, and socioeconomic status, are linked to disparities in ovarian cancer health outcomes such as survival (41) and suboptimal practice patterns delivered to underserved women (42). Transportation issues or travel burden experienced by those outside of urban areas (39) are rarely incorporated into disparities of health outcomes in ovarian cancer trials. As clinical trialists develop more robust recruitment efforts to adequately represent the population of ovarian cancer patients, these key issues should be strongly considered.

In summary, our analysis of a large US ovarian cancer clinical trial demonstrates the important contribution of measuring QOL to assist in identifying on-treatment PROs associated with the likelihood of long-term survival. PROs are increasingly important in ovarian cancer clinical trial design, informing regulatory procedures, and adding prognostic value over clinicopathological factors alone (43,44). Although many have previously identified QOL as prognostic for overall survival, which may be just a matter of months, we believe that recognizing prognostic factors for those who have lived beyond 8 years with this life-threatening illness is very meaningful to the survivor community and may have implications for future treatment considerations. QOL scores, and their change over time, are able to distinguish LTS vs STS, thereby adding clinically meaningful prognostic value in advanced ovarian cancer. Future directions will include development of a long-term survival profile incorporating biologic platforms with patient-reported and clinical factors to improve prognostic accuracy. This direction could directly improve the management possibilities for the majority of advanced ovarian cancer patients.

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Data Availability

The data supporting published research results will be transferred to a public data repository and made available to the public at the time of initial publication.

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