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Patient-reported outcome changes at the end of life in recurrent platinum-resistant ovarian cancer: An NRG oncology/GOG study

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Author contributions

Lari Wenzel is responsible for the concept and design of the article, interpretation of the data, and wrote the manuscript.
Helen Q. Huang performed data analysis and contributed to a critical revision of the manuscript.
Vivian E. von Gruenigen contributed to a critical review of the final manuscript.
David Cella contributed to data interpretation, and a critical revision of the manuscript.
Chelsea O. McKinney contributed to a critical revision of the manuscript.
M. Zevon contributed to a critical review of the final manuscript.
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R.T. Morris contributed to a critical review of the final manuscript.
W. Bradley contributed to a critical review of the final manuscript.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.08.028.

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Abstract

Objectives.—In a prospective study of platinum-resistant ovarian cancer patients, we examined whether the Disease-related Symptoms-Physical (DRS–P) scale of the NCCN/FACT-Ovarian Cancer Symptom Index-18 (NFOSI-18) is responsive to clinical change in patients estimated by their provider to survive at least six months.

Methods.—The NFOSI-18, and other FACT measures, was collected at study entry and 3 and 6 months post-enrollment. Measures were compared for those who died or dropped off study prior to 3 months or prior to 6 months (assumed as health deterioration over time), or those who stayed on study through 6 months (presumed as stable disease over time). Statistical analyses included a fitted linear mixed model for estimating the group differences over time, Cox regression to assess the probability of survival with patient-reported outcomes, and effect size.

Results.—DRS-P scores of patients who completed only one assessment were significantly lower compared to patients who were able to complete two assessments [5.9 points lower (2.0–9.8); $p < 0.01$], or three assessments [8.1 points lower (4.8–11.5); $p < 0.01$]. Measures of abdominal discomfort, functional well-being, emotional well-being, and quality of life were also significant, but treatment side effects were not. Further, in every scale except for neurotoxicity, higher (better) baseline scores were associated with a decreased likelihood of death, after adjusting for age, performance and disease status.

Conclusion.—The NFOSI-18 DRS-P scale is responsive to clinical change. It has potential as an indicator of changing health status with ovarian cancer disease progression, distinct from treatment side effects.

Keywords

Platinum-resistant ovarian cancer; Patient reported outcomes; End of life; NFOSI-18 DRS-P; NRG; End-of life

1. Introduction

Most patients with recurrent ovarian cancer eventually develop platinum resistant disease, defined as disease recurring within 6 months after the last receipt of platinum-based chemotherapy [1]. In this population, treatment after relapse is not curative; it is administered with palliative intent. Several new therapies are currently being investigated to target DNA damage repair and angiogenesis pathways. If effective, these treatments could extend progression free survival (PFS) and even overall survival (OS). In this treatment context, accurate measurement of how patients feel and function can provide important

additional information to assess the overall benefits and risks of cancer therapies [2]. Given the burgeoning new therapies, their accompanying novel toxicities, and the necessity to reduce disease burden, patient-reported outcomes can add considerable value to our understanding of platinum resistant or refractory ovarian cancer.

Although there is a relatively small body of literature examining quality of life (QOL) with recurrent, platinum resistant ovarian cancer, QOL may be maintained for those receiving further chemotherapy, particularly if they are responding to treatment [3]. Among a sample of recurrent, platinum resistant symptomatic patients, 40% derived a clinical benefit from chemotherapy, and 50% reported symptom improvement [4], and patients who received bevacizumab with chemotherapy reported a significantly greater improvement in abdominal symptoms and QOL [5], supporting a role for bevacizumab with chemotherapy in the treatment of women with platinum-resistant ovarian cancer. Moreover, for patients with recurrent or resistant disease, it is likely that as the disease progresses so too does the frequency and severity of disease-related symptoms. While further treatment offers the potential to delay progression, it is often weighed against risk of toxicities. In order to fully appreciate the risks and benefits associated with the potential to delay progression, studies require careful assessment of targeted QOL domains, in particular, disease symptoms, treatment side effects, acceptability of therapy and patient functioning.

In the absence of an OS benefit, it is difficult to placea value upon PFS. On the one hand, delaying cancer progression is likely to confer some benefit to a person's QOL, because of the psychological benefit of knowing one's disease is stable, and because delaying progression is also likely to delay the onset of life-limiting symptoms. On the other hand, treatment itself carries toxicities which can be distressing and life-limiting. In order to fully appreciate the benefits and risks associated with delaying PFS, studies require careful assessment of targeted QOL domains, in particular, disease symptoms, but also treatment side effects, acceptability of therapy and patient functioning. It is hypothesized that a treatment associated with a PFS benefit will also demonstrate a QOL benefit. The reverse is also likely true; that progressive disease is associated with increased frequency and severity of disease-related symptoms.

Developing an appreciation for the natural history of this disease, without emphases on specific cancer treatments, permits us to identify concepts of interest which are likely to be responsive to meaningful treatment benefit. In advanced, recurrent platinum-resistant ovarian cancer, studying the natural history of the disease cannot feasibly or ethically be extracted from the numerous treatment scenarios offered to the majority of women in this situation. It is well known that these patients receive multiple and continuous treatments throughout the advanced disease trajectory until very shortly before death [6]. Therefore, it is difficult to disentangle disease-related symptoms from treatment side effects when attempting to fully understand the natural history of this disease.

We previously prospectively identified quality of life and care needs in patients with persistent or recurrent platinum-resistant ovarian cancer, with the broader mission of improving care goals [7]. The purpose of the study described herein is to determine whether the 9-item Disease-Related Symptoms-Physical (DRS–P) subscale of the 18-item National

Comprehensive Cancer Network FACT Ovarian Symptom Index (NFOSI-18), utilized in the platinum-resistant ovarian cancer care needs study, is a valid aid in detecting likely disease progression in patients with persistent or recurrent platinum-resistant ovarian cancer. A secondary purpose was to evaluate the other subscales of the NFOSI-18 (Treatment Side Effects, Functional Well-Being and Emotional Well-Being) and legacy FACT instruments in this novel patient population.

2. Methods

The study was approved by the Institutional Review Board of all participating GOG institutions. Participants were recruited to a prospective observational study, GOG 0267, assessing the care needs, symptoms, and QOL of patients with platinum resistant or platinum refractory ovarian, fallopian and peritoneal cancers. They were eligible if their life expectancy was considered to be at least 6 months from the date of study enrollment, regardless of current cancer treatment status. All patients who had measurable disease were evaluated using Response Evaluation Criteria in Solid Tumors' (RECIST) guidelines version 1.1 [8]. Current cancer therapy, performance status (PS) and PROs were collected at study entry, and 3 and 6 months.

2.1. Measures

The Disease-Related Symptom-Physical (DRS-P) scale from the NCCN/FACT-Ovarian Cancer Symptom Index-18 (NFOSI-18) [9], is a 9-item scale which comprises the first 9 items of the NFOSI-18. This scale was developed using a qualitative methodology with 50 advanced ovarian cancer patients and 10 expert clinicians. The majority of DRS-P items come from the FACT-O questionnaire [10], but they have been supplemented and reorganized based upon qualitative concept elicitation research and expert input. After establishing that these 9 questions were the most important disease-related symptoms to women with ovarian cancer [9], these questions were further evaluated through cognitive debriefing interviews with 18 women with ovarian cancer to ensure that they were understood as intended.

In addition to the DRS–P, the NFOSI-18 is comprised of 5-item Treatment Side Effects (TSE), 3-item Functional Well-Being (FWB), and 1-item Emotional Well-Being (EWB) subscales. The NFOSI-18 was administered together with the widely-used Functional Assessment of Cancer Therapy-Ovarian (FACT-O) [10], the FACIT-Fatigue [11], FACT/GOG-NTX subscale [12], and the FACT/GOG-Abdominal Discomfort subscale [13]. Psychometric properties of the FACT family of measures have been well-established.

2.2. Statistical Analyses

Patient groups were defined by the time at which they were considered having dropped from the study, which for these analyses corresponded with the number of assessments they completed. Of 102 enrolled patients, 21 patients dropped off study after baseline assessment (completed one assessment), 15 patients discontinued after 3 months (completed two assessments), and 66 patients completed all the three QOL assessments as scheduled at baseline, 3 months and 6 months post study entry. Reasons for study discontinuation

are noted in Table 1, and indicate that study discontinuation was due primarily to death. Therefore, for this paper, we presumed those patients who completed three QoL assessments as having 'stable health status over time', and those who completed one or two QoL assessments as having 'deteriorated health status over time'.

The DRS-P and other measures were examined for differences prior to study discontinuation between patients who were able to complete all 3 assessments, versus 2 assessments, or only 1 assessment, where we made the assumption that assessment completion might serve as a proxy for stable disease (3 assessments) or progressive disease (2 or 1 assessments) during this six month period.

The comparison of the DRS-P subscale score prior to drop off/death was conducted using a linear mixed model. Least square means differences between those who completed one, two, and three assessments respectively were estimated from a fitted linear mixed model and *p*-values were adjusted for multiple comparisons using Hochberg step-up method. Effect sizes were calculated as the estimated least square means difference of the data points at the assessment intervals, divided by the standard deviation (6.12) of the baseline DRS–P. Similar statistical methods were applied to examine performance of the other NFOSI subscales, and the FACT measures. Cox regression analysis was also used to assess the statistical significance of differences in the probability of survival associated with patient-reported outcome scores.

3. Results

3.1. Patient characteristics

Between June 2011 and October 2013, 102 patients completed the baseline assessment. The mean age of participants was 63 years; 89% were white and 96% had a GOG performance status of 0 or 1. At study enrollment, 74% had documented progression of disease, and the majority (83%) were on chemotherapy. After study entry, 32 died within 6 months.

Demographic, disease, treatment, and patient-reported outcomes were compared for those judged to have stable disease or health status over time, compared to those with further health deterioration as defined by "study drop discontinuation" after enrollment. Reasons for study discontinuation are noted in Table 1, and indicate that study discontinuation was due primarily to death.

As indicated in Table 2, the patients who completed one, two, or three QOL assessments were not significantly different on patient characteristics, disease or treatment status, although patients with worse performance status dropped off/died earlier (Fisher's exact test $p = 0.008$). In addition, only one of four patients with a performance status of 2/3 completed all three assessments.

3.2. Disease-related physical symptom differences in patients surviving 3 or 6 months from study entry

The patients who completed only the baseline assessment reported significantly lower DRS-P subscale scores at baseline compared to those who were able to complete two

assessments [5.9 units lower; 95% CI:2.0–9.8; adjusted $p = 0.006$; Effect Size = 0.9], or three assessments [8.1 units lower; 95% CI: 4.8–11.5; adjusted $p < 0.001$; Effect Size = 1.23] (Fig. 1). In addition, Fig. 1 also illustrates that at 3 months post study enrollment the patients who completed only the baseline and 3 month assessment ($N = 15$) reported significantly more disease-related symptoms (lower DRS-P subscale scores) compared to patients who were able to complete all three assessments ($N = 66$) [7 units lower; 95%CI: 3.8–10.1; adjusted $p < 0.001$; Effect Size = 1.07]. Effect sizes for the estimated difference in the DRS-P scores provide evidence of very robust clinically meaningful differences in disease-related symptoms as measured by the DRS–P.

3.3. Disease-related abdominal discomfort differences in patients surviving 3 or 6 months from study entry

The patients reporting the lowest/worst scores on the FACT/GOG-AD scale at baseline had a significantly higher likelihood of death within 6 months, ($p < 0.001$). Fig. 2 illustrates that those patients who completed only the baseline assessment ($N = 21$) reported significantly more abdominal discomfort compared to patients who were able to complete all three assessments (N = 66) [5.6 units lower; 95% CI: 3.5–7.6; adjusted $p < 0.001$], or compared to patients able to complete two assessments ($N = 15$) [3.8 units lower; 95% CI: 1.0. ~6.5; $p = 0.017$].

3.4. Treatment side effects differences in patients surviving 3 and 6 months from study entry

After adjusting for patients' age, performance status, and disease status, as illustrated in Fig. 3, patient-reported treatment side effects, including neurotoxicity, were not statistically significantly different between those patients who were able to complete only the baseline assessment, baseline and 3 month only, or all three (baseline, 3 and 6 month) assessments.

3.5. Functional and emotional well-being differences in patients surviving 3 and 6 months from study entry

After adjusting for patients' age, PS, and disease status, in general, the patients who completed only one assessment reported the lowest/ worst scores on the FWB at baseline. Fig. 4 illustrates that at 3 months post study entry, patients who completed only the baseline and 3 month assessment (N = 15) reported significantly worse functional well-being compared to patients able to complete all three assessments ($N = 66$) [2.4 unites lower; 95% CI: 0.5–4.2; $p = 0.036$]. In addition, those patients who completed only baseline assessment ($N = 21$) reported significantly lower emotional well-being scores than those completing three assessments [0.7 units lower; 95% CI: 0.2–1.2; p = 0.036].

3.6. Quality of life and fatigue differences in patients surviving 3 and 6 months from study entry

We utilized an identical approach to investigate longitudinal differences in QOL and fatigue from legacy FACT measures. Large statistically significant differences were observed across these dimensions, indicating that patients reported the worst QOL and fatigue prior to study drop off or death. (Supplemental panels 1,2,3).

3.7. Survival analysis and all patient-reported outcomes

Cox regression results revealed that with an increasing baseline value in every scale, there is a decreasing hazard associated with death (Table 3). Each scale is statistically significant with the exception of neurotoxicity. For instance, hazard ratios indicate that patients with a one-unit increase in DRS-P at baseline were 9% less likely to die than patients with lower DRS-P scores (95% CI: 0.87–0.94; $p < 0.0001$). Notably, a one-unit increase in FWB was associated with a 20% less likelihood of death at 6 months (95% CI: 0.72–0.89; $p < 0.0001$).

4. Discussion

In this prospective study we tracked the “natural history” of patients with persistent or recurrent platinum-resistant ovarian cancer, specifically to examine whether the Disease-related Symptoms-Physical (DRS–P) scale of the NFOSI-18 could differentiate health status changes likely associated with disease progression versus stabilization in patients estimated by their provider to survive at least six months. The DRS-P does appear to measure disease-related symptoms which are likely to worsen with progressive disease. We state this with confidence because the treatment side effect and neurotoxicity measures do not show the same prediction as DRS–P, fatigue or abdominal discomfort, i.e., DRS-P measures disease more than treatment, and the TSE measures treatment more than disease. Further, the robust effect sizes provide validation for clinically meaningful between-group differences as disease is presumed to progress or stabilize. Moreover, the effect sizes exceed minimally important differences (MIDs), which have been defined as a difference in a score that is large enough to have implications for a patient’s treatment or care [14].

It is reasonable to question whether treatment side effects can be disentangled from the DRS-P scale. This is an important question with respect to platinum-resistant, recurrent ovarian cancer, since this patient population receives multiple cancer treatments over time while they face a poor prognosis. In this study 90% of patients at baseline were receiving chemotherapy, and for those surviving, proportions treated did not fall below 80% [7]. Both disease symptoms and treatment side effects are a part of the natural history of advanced ovarian cancer; a disease which can be heavily treated until shortly before death. Notably, the DRS-P did document statistically and clinically meaningful changes over time, while the treatment side effects scale did not differ between those with or without progressing disease, again indicating that the DRS-P can discriminate between disease and treatment symptoms, and is presumed to be sensitive to disease progression, thereby opening an additional avenue to measure treatment response. The reverse may also be true, where clearly declining scores could inform a shift away from chemotherapy at the end of life (EOL), to further support high-value EOL care as noted by Fang et al. [15].

Inclusion of QOL assessments in recurrent ovarian clinical trials are highly valued, since a positive treatment response may be evident on radiographic assessment, serial CA-125 s and greater symptom improvement as reported by the patient. Use of a focused QOL measure can enhance clinical outcome assessment, reduce patient and institutional burden, and importantly, improve patient care. This type of focused QOL measure may be of particular interest to those seeking FDA label claims or are otherwise developing novel cancer treatments. Nevertheless, the equally strong differences displayed in legacy measures

also indicate that we are in a position not only to elucidate the “natural history” of recurrent, platinum resistant stable or progressive disease, regardless of ongoing treatment type or duration, but also address QOL concerns which patients consider important [16,17].

This observational report has several limitations. First, this report lacks documentation of a treatment and supportive care history, as that was beyond the scope of this observational study. Such information would have been useful in determining how active cancer treatment and/or palliative care measures may have affected the patient-reported outcomes. Further, it is acknowledged that cancer treatments (e.g., PARP inhibitors) as well as the management of treatment toxicities and symptoms of disease progression have continued to evolve since the initiation of this study. However, these advancements would not be expected to diminish the ability of the DRS-P to discriminate between symptoms of disease progression and treatment toxicities. In addition, health deterioration, or progressing disease, was assumed to be the reason for study discontinuation. This assumption was made since study dropout was almost entirely attributable to death, and in this population, death is almost always due to progressing disease (versus treatment, or other causes). We further verified this through univariate analyses with vital status and the number of assessments completed. Therefore, the number of assessments completed was also considered an indicator of study drop off, which is highly correlated with survival. However, this can only be confirmed by validating these data through further analyses examining longitudinal relationships between the DRS-P scale and documented disease noted as complete or partial response, or stable or progressive disease as confirmatory clinically relevant anchors. The observational nature of this trial design did not permit examination of these clinical anchors. Further, since these post hoc analyses were considered exploratory, no significance level was pre-specified and no adjustments were made for multiple tests.

This study presents a new, brief measure of physical disease-related symptoms specific to ovarian cancer, together with the established FACT-O-TOI, which performed well in this setting and was also able to presumably discern stable versus progressing disease longitudinally. The DRS-P longitudinal changes were also supported by similar changes in measurements of abdominal discomfort, fatigue, and quality of life, measured by the FACT-O total score. While the DRS-P provides a briefer and more parsimonious assessment of disease-related symptoms, this does not suggest that other measures are not reliable or valid in measuring changes associated with disease progression, or response to treatment. In short, selection of measures will depend on the study purpose, but for investigators who want primarily to capture the natural history of advancing ovarian cancer based on the patient’s experience of physical symptoms, the DRS-P is well-suited for that purpose.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- The DRS-P scale can distinguish ovarian cancer changes in health status with disease progression versus stabilization.
- The DRS-P scale can identify ovarian cancer changes in health status that are distinct from treatment side effects.
- The DRS-P can capture symptoms and functional aspects of the natural history of advancing ovarian cancer.
- Assessment completion and survival time are highly correlated.

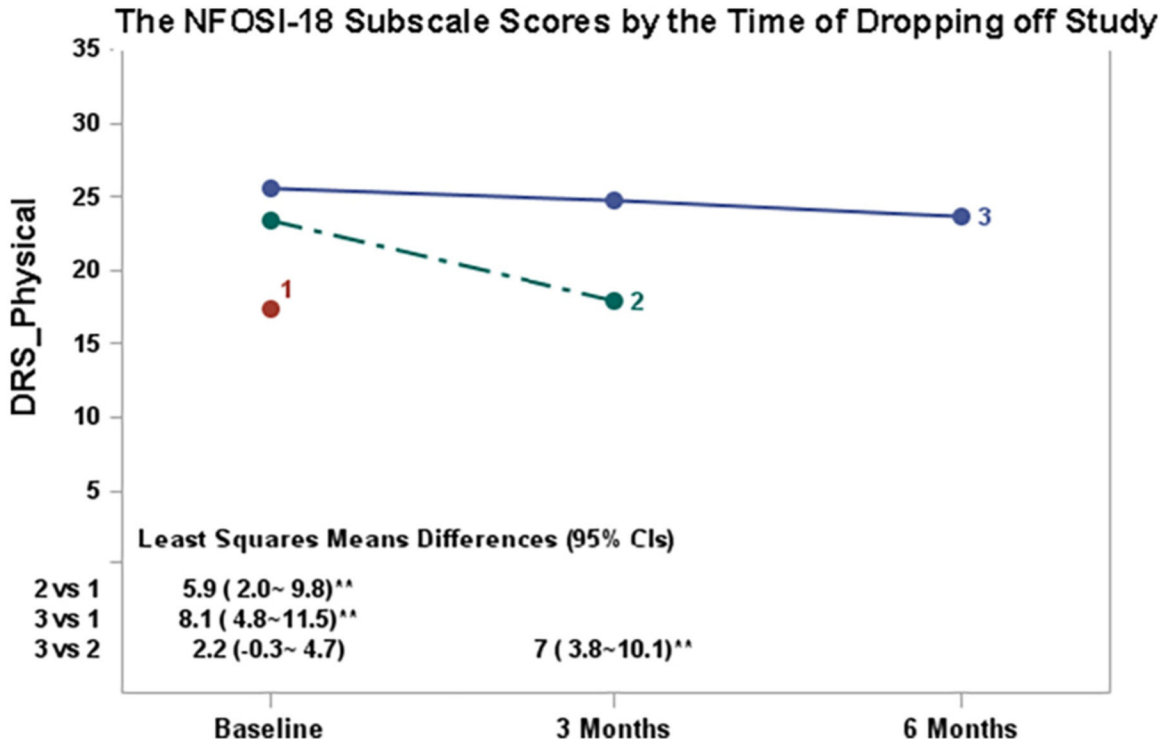

Fig. 1.

Disease-Related Symptoms - Physical Longitudinal Differences. Patient reported QOL and symptom scores in each group are displayed in the figures. The group differences are the least squares means differences accompanied with 95% CI in brackets. *: indicates adjusted *p*-value<0.05; **: indicates adjusted p-value<0.01.

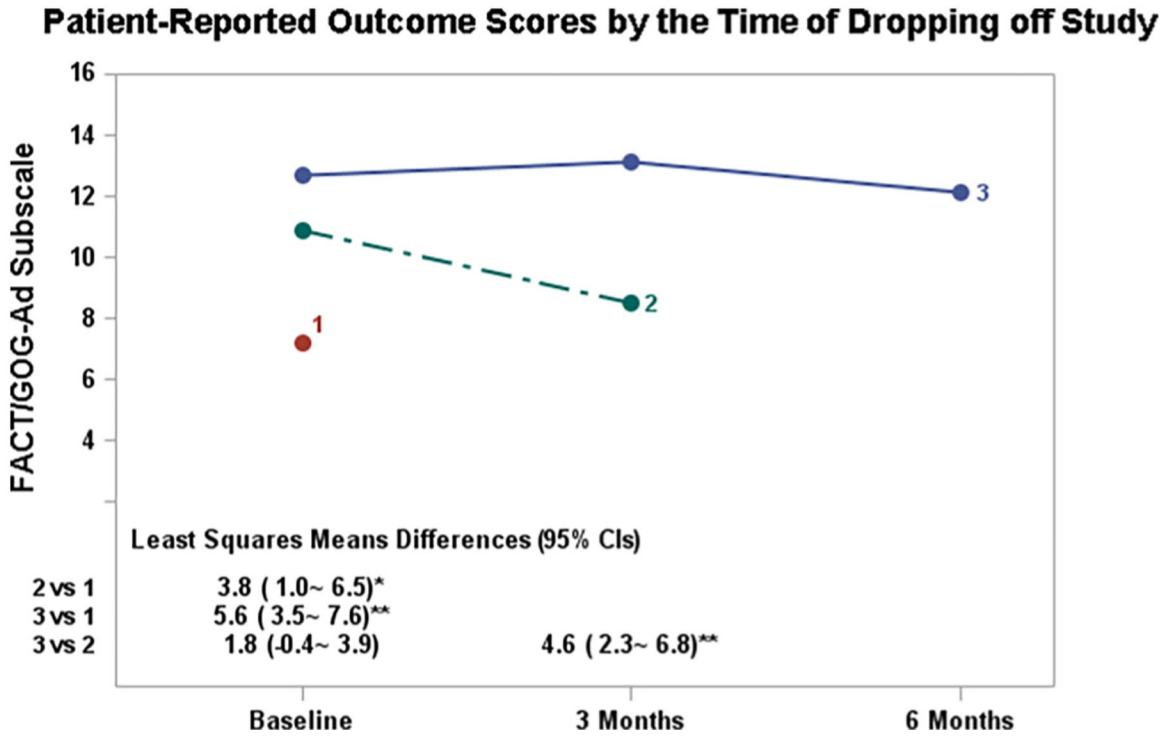

Fig. 2.
Abdominal Discomfort - Longitudinal Differences.

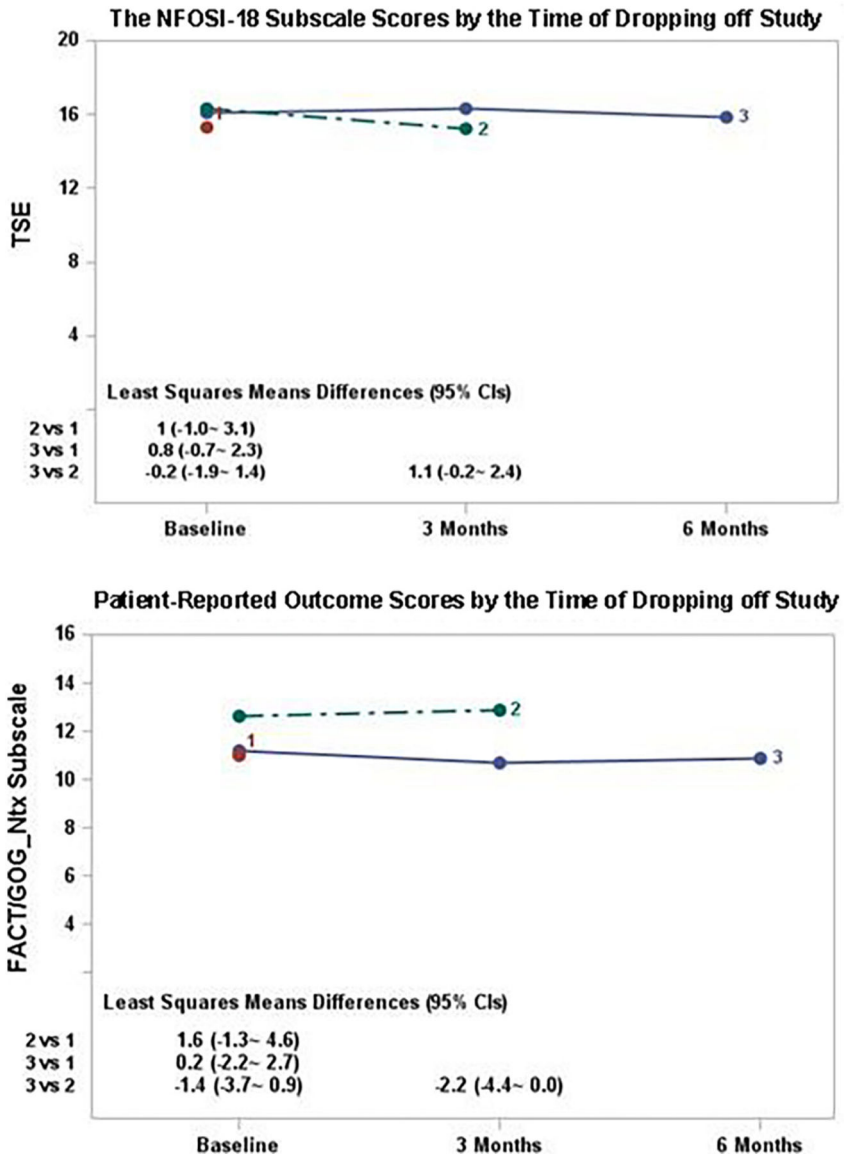

Fig. 3.

Treatment Side Effects & Neurotoxicity - Longitudinal Differences.

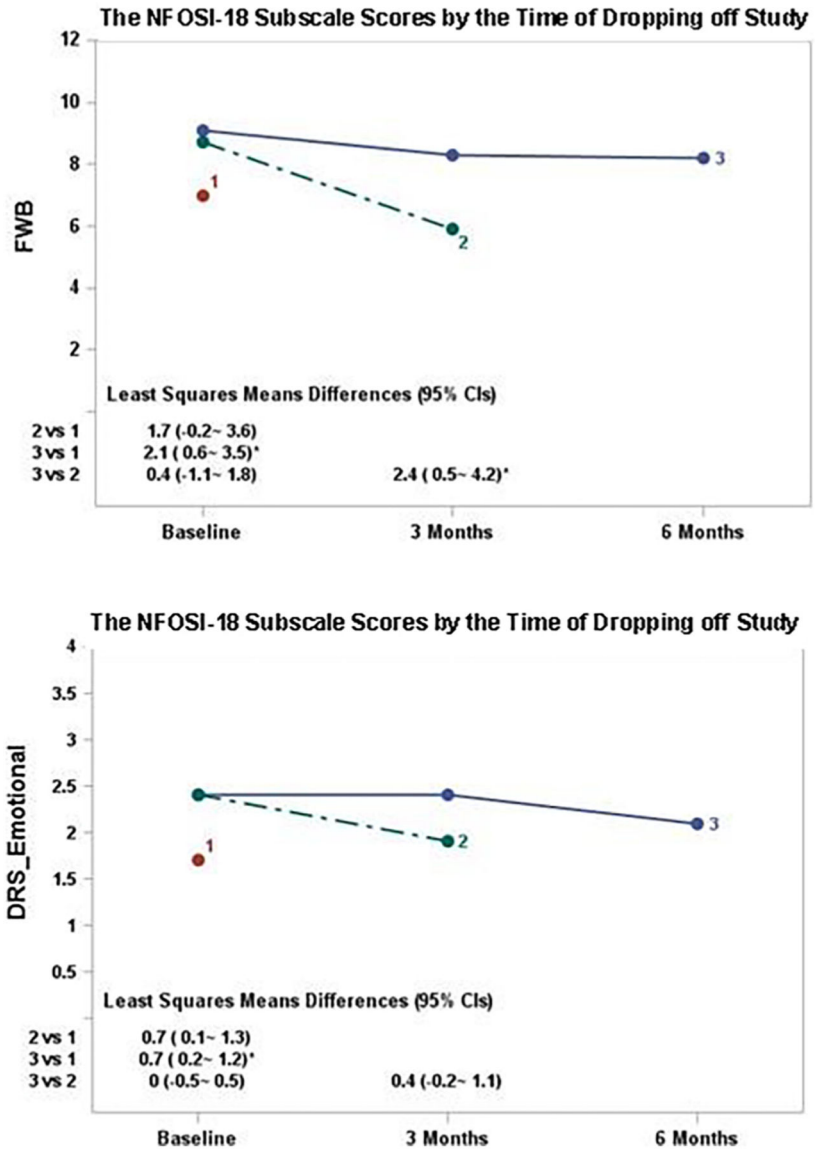

Fig. 4.

Functional & Emotional Well-being – Longitudinal Differences.

Table 1

Reasons for Study Discontinuation.

Study Discontinuation Reasons	PRO Assessments Completed	
	One assessment (N = 21)	Two assessments (N = 15)
Death	16	14
Patient was too sick	2 (one died after 3 months	0
Administration error	1 (died after 3 months)	0
Patient declined	1	1
Loss to follow-up	1	0

Table 2

Assessments Completed by Patient Characteristics.

		One assessment N = 21		Two assessments N = 15		Three assessments N = 66	
Characteristic	**Category**	**N**	**%**	**N**	**%**	**N**	**%**
Age (yrs)	Mean	62.4		67.3		63.2	
Age Group	<50	3	14.3	1	6.7	10	15.2
	50–59	4	19.0	3	20.0	14	21.2
	60–69	9	42.9	5	33.3	25	37.9
	≥ 70	5	23.8	6	26.7	17	25.7
Race	White	20	95.2	13	86.7	58	87.9
	Other	1	4.8	2	13.3	8	12.1
Performance Status	0	6	28.6	8	53.3	44	66.7
	1	12	57.1	7	46.7	21	31.8
	2/3	3	14.3	0	0	1	1.5
Marital Status	Married/living with partner	12	57.1	11	73.3	39	59.1
	Single/Divorced/Widowed	9	42.9	4	26.7	27	40.9
Employment	Employed or self employed	6	28.6	3	20.0	29	44.0
	Not employed or disabled	7	33.3	4	26.7	14	21.2
	Retired	8	38.1	8	53.3	23	34.8
Disease Status	Progression/Partial regression	18	85.7	13	86.7	49	74.2
	Stable	2	9.5	2	13.3	11	16.7
	Unknown	1	4.8	0	0	6	9.0
Therapy	Chemotherapy	19	90.5	12	80.0	54	81.8
	Other care or none	2	9.5	3	20.0	12	18.2

Table 3

Multivariate Cox model for Death with Patient-Reported Outcomes.

		95% Confidence Interval			
Model	**Independent Variable**	**HR***	**Lower**	**Upper**	**p-value**
1	NFOSI – DRS-P	0.905	0.867	0.944	< 0.0001
1	NFOSI – DRS-E	0.745	0.594	0.934	0.011
3	NFOSI – TSE	0.828	0.744	0.921	0.001
4	NFOSI – FWB	0.801	0.72	0.893	< 0.0001
5	FACT-O	0.969	0.955	0.983	< 0.0001
6	FACIT-F	0.968	0.949	0.988	0.002
7	FACT-NTX	1.034	0.965	1.107	0.344
8	FACT-AD	0.88	0.834	0.929	< 0.0001

*Hazard Ratios in all models adjusted for age, performance status and disease status.