Measure of Ovarian Symptoms and Treatment concerns (MOST) indexes and their associations with health-related quality of life in recurrent ovarian cancer.

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Abstract

Purpose

The Measure of Ovarian Symptoms and Treatment (MOST) concerns is a validated patient-reported symptom assessment tool for assessing symptom benefit and adverse effects of palliative chemotherapy in women with recurrent ovarian cancer (ROC). We aimed to examine (i) the co-occurrence of symptoms within MOST symptom indexes and (ii) the association between MOST symptom indexes and key aspects of health-related quality of life (HRQL).

Method

A prospective cohort of women with ROC completed the MOST-T35, EORTC QLQ-C30 and EORTC QLQ-OV28 at baseline and before each cycle of chemotherapy. Analyses were conducted on baseline and end-of-treatment data. Exploratory factor analysis and hierarchical cluster analysis identified groups of co-occurring symptoms. Path models examined associations between MOST symptom indexes and HRQL.

Results

Data from 726 women at baseline and 681 at treatment-end who completed all 22 symptom-specific MOST items and at least one HRQL measure were analysed. Four symptom clusters emerged at baseline and treatment-end: abdominal symptoms, symptoms associated with peripheral neuropathy, nausea and vomiting, and psychological symptoms. Psychological symptoms (MOST-Psych) and symptoms due to disease (ovarian cancer) or treatment (MOST-DorT) were associated with poorer scores on QLQ-C30 and OV28 functioning domains and worse overall health and/or quality of life at both time points.

Conclusion

Four MOST symptom clusters were consistent across statistical methods and time points. These findings suggest that routine standardised assessment of psychological and physical symptoms in clinical practice with MOST plus appropriate symptom management referral pathways is an intervention for improving HRQL that warrants further research.

Introduction

After completion of first-line treatment for ovarian cancer, the majority of women will eventually relapse and be offered palliative chemotherapy [1]. Women with recurrent ovarian cancer (ROC) commonly experience high symptom burden due to disease progression and cumulative toxicity caused by prior chemotherapy particularly in those with platinum resistant /refractory disease as well as patients with potentially platinum sensitive ROC who have had multiple lines of prior treatment[2]. The aim of treatment for ROC is to palliate disease-related symptoms, improve health-related quality of life (HRQL), and delay disease progression, with acceptable toxicity [3]. Hence, the benefits of treatment for symptom control need to be carefully balanced against the adverse effects of treatment. However, the extent to which symptoms improve in response to palliative chemotherapy is rarely assessed, documented, or included in reports of clinical trials [2, 4]. Moreover, if ovarian cancer-specific patient-reported outcome measures (PROMs) combine symptoms caused only by ovarian cancer together with symptoms caused only by chemotherapy into a single PROM score, this distorts and conflates the net benefits and burdens of chemotherapy[5].

The Measure of Ovarian cancer Symptoms and Treatment concerns (MOST) was developed in response to a call for the development and validation of a fit-for-purpose PROM to assess symptom benefit and the adverse effects of chemotherapy in women with ROC that could be incorporated as an endpoint in Gynecologic Cancer Intergroup (GCIG) trials [6]. The GCIG-Symptom Benefit Study (GCIC-SBS Stage 1) led to the development of the first version of MOST (MOST-T35, with 35 items) [5], subsequently revised to 24 items (MOST-T24) in GCIG-SBS Stage 2 and validated for use in clinical trials [7]. GCIG, an international collaborative of gynaecological cancer clinical trials groups, currently recommends the inclusion of MOST in clinical trials of palliative chemotherapy in ROC to assess symptom benefit and treatment burden [8].

MOST-T24 generates five index scores comprising abdominal symptoms, chemotherapy-related side-effects, other symptoms caused either by ROC or its treatment, psychological symptoms, and overall well-being. MOST indexes were created using a formative approach to determining suitable content and scoring rules [9], that is, items were selected for their clinical relevance and combined into clinically meaningful categories and did not need to be correlated within an index [9, 10]. However, this approach did not yield insight into whether symptoms within MOST indexes co-occur and how they relate to each other. Understanding the interrelationship between symptoms within MOST indexes would be useful from a clinical perspective to enable more targeted symptom management interventions.

While MOST is informative for assessing the impact of treatment for ROC on symptoms and overall well-being, it is not a measure of HRQL and was never intended to be as there were already several widely used instruments to measure HRQL. HRQL is a broad, multi-dimensional construct encompassing perceptions of core functions (e.g. physical, emotional, social & cognitive), as well as symptoms of disease and treatment [11]. The Wilson and Cleary conceptual model of HRQL posits that symptoms caused by disease and treatment influence functional status which, in turn, influences perceptions of general health and overall HRQL [12]. Investigators wishing to assess HRQL in ROC clinical trials are

advised to administer MOST-T24 in combination with an ovarian cancer-specific HRQL measure such as the EORTC QLQ-OV28 [13] or FACT-O [14]. However, minimising patient burden is an important consideration in trials of treatments for advanced disease, and limiting questionnaire length can help to avoid problems caused by missing patient-reported outcome data [15]. In trials or in the clinic where MOST is administered alone, understanding how MOST symptom indexes relate to HRQL domains would aid interpretation of MOST scores and enable inferences about the likely impacts of treatment on HRQL.

Using data from GCIG-SBS Stage 2, the objective of this analysis was to examine: (i) the co-occurrence of symptoms within MOST symptom indexes; and, (ii) the association between MOST symptom indexes and key aspects of HRQL.

Method

GCIG-SBS Stage 2 study design

The primary aim of GCIG-SBS Stage 2 (ANZCTR 12607000603415) was to determine the proportion of women benefitting from palliative chemotherapy as defined by a clinically significant improvement in HRQL scores and improvement of symptoms. GCIG-SBS Stage 2 was a prospective cohort study of women with platinum-resistant or platinum-refractory ROC (PRR-ROC) as well as a cohort with potentially platinum sensitive recurrent ovarian cancer (PPS-ROC) receiving three or more lines of chemotherapy. Eligibility criteria were progression based on CA125 level, imaging, or clinical symptoms; Eastern Cooperative Oncology Group performance status 0–3; life expectancy > 3 months; and ability to self-complete PROMs. Patients were recruited from 120 sites in 11 countries. Ethics approval was obtained at all participating sites and written informed consent was obtained from all participants.

Participants completed PROMs on paper at each clinic visit prior to seeing their physician. The following PROMs were completed at baseline (i.e. before starting their next line of chemotherapy) and every 3–4 weeks before each cycle of chemotherapy, until disease progression:

MOST-T35 [5] consists of 35 items that assess symptoms, treatment-related concerns and well-being during the last 3-4 weeks. Symptoms/concerns are rated on a scale from (0) no trouble at all to (10) worst I can imagine; well-being is rated from 0 (worst possible) to 10 (best possible). A subset of 24 items can be scored into 5 indexes[7]: abdominal symptoms (MOST-Abdo, 2 items), disease or treatment-related symptoms (MOST-DorT, 11 items), chemotherapy-related symptoms (MOST-Chemo, 6 items), psychological symptoms (MOST-Psych, 2 items) and well-being (MOST-Wellbeing, 3 items). MOST indexes are scored by computing the average of the component items and rescaling to 0-100, with higher scores representing worse symptom burden/better well-being. For the purpose of the present analyses focusing on symptoms and their association with HRQL, only the 4 symptom-specific MOST indexes were included (i.e. 21 items) plus 1 item (MOST-T35 item #31) assessing “trouble concentrating”, summing to 22 items in total.

EORTC QLQ-C30 is a well-validated, widely used cancer-specific HRQL measure [16, 17]. It consists of 30 items assessing five functioning domains (i.e. physical, role, emotional, cognitive and social functioning),

8 common symptoms (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea), financial difficulties, overall health and quality of life.

EORTC *QLQ-OV28* is an ovarian-cancer specific module [13], designed to supplement the EORTC QLQ-C30 in clinical trials. It consists of 28 items assessing 7 domains: abdominal/gastro-intestinal symptoms, peripheral neuropathy, other chemotherapy side-effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment and sexual functioning.

Given MOST provides comprehensive coverage of OC-relevant symptoms, we only included functioning domains from the EORTC QLQ-C30 (i.e. physical, social, role functioning) and QLQ-OV28 (i.e. body image, attitude to disease and treatment, sexual functioning) in analyses examining associations between MOST symptom indexes and key aspects of HRQL. We also excluded QLQ-C30 emotional and cognitive functioning domains from analyses due to similarity of item content with MOST-Psych and MOST-T35 item #31 "trouble concentrating" to avoid issues of multi-collinearity in multivariable models. See Table S1 in the supplementary file for an overview of overlapping item content, justifying this decision.

Statistical analysis

All analyses described below were conducted using: (i) the first MOST completed at "baseline" i.e. before starting next line of chemotherapy and (ii) the last MOST completed during treatment.

To address our first aim, two statistical approaches were used:

Exploratory factor analysis (EFA) was performed on the 22 symptom-specific MOST items to identify groups of interrelated symptoms and their underlying factor structure. EFA was performed with principal axis factor extraction and oblimin rotation. The number of factors extracted was guided by examination of the scree plot and eigenvalues greater than 1 [18]. Velicer's minimum average partial (MAP) test and parallel analysis [19] were performed to confirm the number of factors or "clusters". The criterion for inclusion in a symptom cluster was a factor loading above .40 [20].

Hierarchical cluster analysis (HCA) was also performed to identify symptom clusters. This method groups similar clusters together and separates them from other clusters. HCA was conducted with single linkage and Euclidean distance as the similarity measure. The dendrogram generated by each HCA analysis was evaluated to determine which symptom to allocate to each cluster. The distance at which the branches join in the dendrogram indicates similarity, with shorter branches indicating greater similarity. Because SPSS presents similarity as rescaled distances rather than correlations, we used two arbitrary thresholds for the interpretation of symptom clusters: one lower (rescaled distance <10) and one higher (rescaled distance <15).

To address our second aim, path models were tested with maximum-likelihood as an estimation method. Drawing on Wilson and Cleary's model [12], the QLQ-C30/OV28 functioning domains were modeled as mediators of the associations between MOST symptom indexes and QLQ-C30 overall health

and quality of life, and QLQ-C30 overall health was modeled as a mediator of associations between MOST symptom indexes and QLQ-C30/OV28 functioning domains with overall quality of life. All direct and indirect paths were estimated. A graphical representation of the path model tested is displayed in Figure S1 in the supplementary file. Model fit was assessed by the comparative fit index (CFI), the standardized root mean square residual (SRMR), and the root mean square error of approximation (RMSEA) [21, 22].

EFA and HCA were performed using SPSS version 24; path models were testing using Mplus 7.

Results

Analyses included the 762 women at baseline (of 948 who completed baseline assessments) and 681 during treatment (of 828 who completed on-treatment assessments) who completed all 22 symptom-specific MOST items, plus at least one HRQL measure (Table 1). On average, the 681 questionnaires during treatment were completed 22 days (range 0 to 389) before the end of treatment. At baseline, the characteristics of women included versus excluded due to missing MOST items/HRQL assessments did not differ significantly (Table 1). However, a significantly larger proportion of older women were excluded from treatment analyses due to missing data.

Co-occurrence of symptoms within MOST Symptom indexes.

Exploratory factor analysis (EFA) and Hierarchical Cluster Analysis (HCA) at baseline. The overall Kaiser-Meyer-Olkin test = 0.88 and Bartlett's test were significant (p <.0001 indicating that an EFA could be supported by the data. Five factors had eigenvalues greater than 1.0, accounting for 57% of the variance. In contrast, Velicer's MAP test and parallel analysis indicated a 3 and 4-factor model, respectively. For this reason, we conducted two additional EFA's with principal axis factor extraction, specifying a 3 and 4 factor solution, to examine the factor loadings of the 22 items.

A summary of the results from the 3, 4, and 5 factor EFA's are displayed in Table 2. The symptom clusters that emerged most consistently across solutions were: 1) 'abdominal swelling, bloating and/or fullness', 'abdominal pain, discomfort and/or cramps' and 'fatigue'; 2) 'numbness or pins and needles' and 'sore hands and feet'; 3) 'nausea', 'vomiting', 'indigestion' and 'trouble eating'; and, 4) anxiety', 'depression' and 'trouble concentrating'.

Results from the HCA at baseline are also summarised in Table 2 and illustrated in the dendrogram (Figure 1). Using the lower threshold (<10 rescaled distance), two symptom clusters were observed: 1) 'sore mouth or throat', 'difficulty swallowing', and 'skin rash'; and, 2) 'nausea' and 'vomiting'. Using the higher threshold (<15 rescaled distance), four clusters were observed: 1) 'sore mouth or throat', 'difficulty swallowing', and 'skin rash'; 2) 'nausea', 'vomiting' and 'indigestion'; 3) 'anxiety' and 'depression' and; 4) 'abdominal swelling, bloating and/or fullness', 'abdominal pain, discomfort and/or cramps'. Four symptoms ('hair loss', 'bladder problems', 'trouble sleeping' and 'shortness of breath') did not meet the criterion for inclusion in a symptom cluster in the EFA or HCA analyses.

EFA and HCA during treatment. The EFA similarly identified five factors with eigenvalues greater than 1, accounting for 59% of the variance (Kaiser-Meyer-Olkin test = 0.89; Bartlett's test $p < .0001$). However, Velicer's MAP test and parallel analysis indicated models with 4-factors or 3-factors, respectively. Using the same approach described above, two additional EFA's were conducted to examine the factor loadings of these alternative solutions. Results from the 3, 4, and 5 factor EFA's (Table 2), indicated the symptom clusters that emerged most consistently were: 1) 'abdominal swelling, bloating and/or fullness', and 'abdominal pain, discomfort and/or cramps'; 2) 'numbness or pins and needles' and 'sore hands and feet'; 3) 'sore mouth or throat', 'difficulty swallowing'; 4) 'nausea' and 'vomiting'; and, 5) anxiety', 'depression' and 'trouble concentrating'.

Results from the HCA during treatment are also summarised in Table 2 and illustrated in the dendgrogram (Figure 2). Using the lower threshold (<10 rescaled distance) five clusters were observed: 1) 'anxiety' and 'depression'; 2) 'abdominal pain, discomfort and/or cramps' and 'abdominal swelling, bloating and/or fullness'; 3) 'sore mouth or throat', 'difficulty swallowing' , 'skin rash' and 'bladder problems'; 4) 'nausea' and 'vomiting', and; 5) 'sore hands and feet' and 'numbness or pins and needles'. Using the higher threshold (<15 rescaled distance) two clusters were observed: 1) psychological symptoms plus trouble concentrating, abdominal symptoms, 3 chemotherapy-related and 9 disease or treatment related symptoms, and; 2) symptoms of peripheral neuropathy. Two symptoms ('hair loss' and 'trouble sleeping') did not meet the criterion for inclusion in a symptom cluster in either the EFA or HCA analyses.

Associations between MOST symptom indexes and HRQL

Given the EFA and HCA indicated trouble concentrating clustered fairly consistently with anxiety and depression, in the path models we included this item in addition to anxiety and depression in the MOST-Psych index. The two peripheral neuropathy symptoms 'sore hands and feet' and 'numbness or pins and needles' also predominantly clustered together, separate to the other chemotherapy-related symptoms. As a result we revised the scoring of the MOST-Chemo index by removing these two items, and scoring them separately in a new index labeled 'MOST-NTx'. In the path analyses that followed, these revised index scores for MOST-Psych, MOST-NTx and MOST-Chemo were included, in addition to MOST-Abdo and MOST-DorT scored using their original scoring algorithms. Of note, in the path models all paths between predictor, mediator and outcome variables were estimated simultaneously. As such, the observed coefficients represent unique associations over and above the other predictor variables included in the model.

Results from the first path model examining associations at baseline are summarised in Table 3. Higher MOST-Abdo scores were associated with poorer social and role functioning, body image, attitude to disease and treatment, and worse overall health. Higher MOST-DorT scores were associated with poorer physical, social, and role functioning; and, worse overall health. Higher MOST-Chemo scores were associated with poorer body image and attitude to disease and treatment, while higher MOST-NTx

scores were associated with poorer physical functioning. Higher MOST-Psych scores were associated with worse scores on all outcomes, except for physical functioning and overall health.

MOST-Abdo was indirectly associated with overall quality of life via role functioning and overall health (β= -.04, p<.0001), whereas MOST-NTx was indirectly related to overall quality of life via physical functioning and overall health (β= -.01, p=.029). MOST-DorT was indirectly related to overall quality of life via physical (β= -.04, p= .005), social (β= -.02, p<.0001), role functioning (β= -.06, p< .0001) and overall health, while MOST-Psych was indirectly associated with overall quality of life via social (β= -.01,p= .022), role functioning (β=-.02, p= .010), attitude to disease and treatment (β=-.03, p= .04), and overall health.

Results from the second path model examining associations during treatment are displayed in Table 4. Higher MOST-DorT scores were associated with poorer physical, social and role functioning, attitude to disease and treatment and overall health. Higher MOST-Psych scores were associated with worse scores on all outcomes except overall quality of life. Higher MOST-Abdo scores were associated with poorer overall health. MOST-NTx and MOST-Chemo were not associated with any of the outcomes.

During treatment MOST-DorT was indirectly associated with overall quality of life via role functioning and health status (β=-.10, p<. 0001). MOST-Psych was indirectly related to overall quality of life via role functioning (β=-.02,p= .026), body image (β=-.02, p= .019), attitude to disease and treatment (β=-.04,p= .020) and overall health.

We also conducted supplementary analyses to examine an alternative model at both time points that additionally included the QLQ-C30 cognitive and emotional functioning domains as mediators of the associations between MOST symptom indexes and key aspects of HRQL. The results of these path models are displayed in supplementary Table S2 and S3. Results from these models were consistent with previous models, with the exception that the direct associations between MOST-Psych and overall quality of life at baseline; and, overall health during treatment, were no longer significant.

Finally, we performed post-hoc analyses to examine the correlation between the MOST-Wellbeing index and the QLQ-C30 global QOL domain. Results indicated a moderate to strong correlation between these scales at baseline (r = .68, p<.001) and end of treatment (r = .74, p<.001).

Discussion

MOST is a fit-for-purpose PROM specifically developed to assess symptom benefit and adverse effects of treatment in clinical trials of palliative chemotherapy for ROC. This study examined the co-occurrence of symptoms within MOST symptom indexes and their association with key aspects of HRQL. Four symptom clusters emerged consistently at two time points across different statistical techniques: abdominal symptoms, symptoms of peripheral neuropathy, nausea and vomiting, and psychological symptoms. Psychological symptoms (MOST-Psych) and symptoms that could be caused by either ovarian cancer or treatment (MOST-DorT) were consistently associated with poorer scores on QLQ-C30 and

OV28 functioning domains, as well as worse overall health and/or overall quality of life, both before and at the end of treatment.

The identification of co-occurring symptoms is useful for informing symptom management and directing supportive care in clinical practice. The identification of one symptom within a cluster (e.g. anxiety) may prompt investigation of associated symptoms (e.g. depression and perceived cognitive deficits) through clinical interview and discussion with the patient. Another benefit of identifying groups of co-occurring symptoms is that treatment of one symptom may alleviate other symptoms in a cluster if a particular symptom is affected by another symptom in the cluster (e.g. nausea and vomiting), or if they share a common etiology [23, 24]. However, symptoms that co-occur but do not share a common pathophysiology may require different targeted interventions [23].

Psychometrically, the symptom clusters identified closely align with the composition of the validated MOST symptom indexes [7]. However, our findings suggest two possible modifications to these index scores. Firstly, 'trouble concentrating' frequently co-occurred with anxiety and depression suggesting it could be included as part of the MOST-Psych index. This finding is supported by several previous studies demonstrating that self-ratings of cognitive dysfunction are closely correlated with self-ratings of anxiety and depression [25]. Secondly, the two symptoms of peripheral neuropathy assessed by MOST ('numbness or pins and needles' and 'sore hands and feet') consistently clustered separately to the other chemotherapy-related symptoms. As such, these two symptoms could be removed from the MOST-Chemo index, scored separately and labeled 'MOST-NTx'. This modified scoring approach for MOST-Chemo/MOST-NTx has recently been adopted in the development of a new version of MOST designed for surveillance of symptoms following first line treatment for ovarian cancer [26].

In multivariable path analyses, associations were consistently observed between psychological symptoms (MOST-Psych) and almost all HRQL domains at both time points, highlighting the potential importance of psychological support throughout treatment. A previous study of women with ROC similarly showed anxiety and depression were both associated with poorer scores on all QLQ-C30 functioning domains and global health at baseline and after chemotherapy [27]. A meta-analysis also indicated women with ovarian cancer were almost twice as likely to experience clinically significant depression and more than four times as likely to experience clinically significant anxiety at some point in treatment, compared to healthy women [28]. These findings emphasise the potential benefits of routine screening for psychological distress in clinical practice with appropriate referral for psychological intervention to improve HRQL [29]. To facilitate triaging for psychological support, threshold scores have recently been identified for MOST items that signify clinically important anxiety and depression. Specifically, scores above 3 on 'depression (feeling sad)' and 4 on 'anxiety (feeling worried)' indicate clinically important symptoms requiring further assessment/referral by the treating oncologist [26].

Associations were also apparent between symptoms that could be caused by either disease or treatment (MOST-DorT), and poorer physical, social and role functioning and worse overall health at both time points. MOST-DorT includes symptoms such as fatigue, trouble sleeping, indigestion, diarrhoea, nausea, vomiting, trouble eating, constipation & shortness of breath. Given their association with poorer HRQL, these findings highlight the potential for routine assessment of these physical

symptoms in clinical practice with appropriate referral pathways for intervention. Of note, associations between abdominal symptoms (MOST-Abdo) and poorer functioning scores were only apparent at baseline and not during treatment. This may have arisen because relief of abdominal symptom provided by chemotherapy [7] weakened negative associations with HRQL at the end of treatment.

MOST is ideally suited to quantify the symptom benefit versus treatment burden of palliative chemotherapy for ROC, focusing exclusively on symptoms and global well-being. Researchers or clinicians wishing to assess functioning (e.g. social or role functioning) or other aspects of HRQL (e.g. body image, sexuality, attitude to disease and treatment) should administer the MOST in combination with the EORTC-QLQ-C30[16] and QLQ-OV28[13] or other measures of HRQL. However, as the EORTC recommends use of the QLQ-C30 in conjunction with the QLQ-OV28, the length of these questionnaires (58 items) may prohibit their use in contexts where respondent burden needs to be minimised such as in routine clinical practice. The MOST-Wellbeing index displayed moderate-to-strong correlations with the QLQ-C30 global QOL domain and may provide a pragmatic assessment of 'Global QOL' in contexts where limiting PROM length is desirable.

The strengths of this study include the use of a validated, fit-for-purpose PROM to assess the co-occurrence of symptoms and their association with HRQL in a large, international sample of women with ROC at two time points. However, the cluster analytical approach used did not yield any insights into the underlying causes of co-occurring symptoms. As such, the alleviation of one symptom may not necessarily lead to the alleviation of other symptoms in an identified cluster. In addition, the path models tested examined correlations between MOST symptom indexes and key aspects of HRQL, precluding any causal inferences about the direction of these associations. Furthermore, symptom clusters and their association with HRQL may change depending on the disease and/or treatment stage so these results may not be applicable to women with earlier stage disease or to those at a different point in the treatment trajectory; this issue could be further explored in future research.

In conclusion, using the MOST we identified four symptom clusters in a large sample of women with ROC that were consistent across statistical methods and time points. Psychological symptoms and symptoms that could be caused by either disease or treatment were most consistently associated with poorer functioning, health status and/or overall quality of life. Understanding the interrelationships between symptoms within MOST indexes and their association with HRQL may help to direct symptom management and supportive care. Routine screening of symptoms in clinical practice using the MOST with appropriate referral pathways to address troublesome symptoms may help alleviate symptom burden and improve the HRQL of women with ROC.

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Conflict of interest

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Contribution to authorship

RC, MTK, DC, MRS, YCL, FR & MF conceptualization of the study; AL, FJ, FH, AO, JB, AO, JB, JL, DB, AF, ROC, KD & MCK patient recruitment, data acquisition and management; RC, DC, MK, MRS, MF data analysis and interpretation; RC – original draft; all authors writing rerview & editing.

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Table 1. Baseline Characteristics of women included/excluded in analyses at baseline and during treatment

	Included in baseline analyses n (%)	Excluded from baseline analyses n (%)	*p*	Included in treatment analyses n (%)	Excluded from treatment analyses n (%)	*p*
Total n	762	186		681	147	
Age (years), mean (SD)	62.2 (10.5)	63.8 (11.1)		62.1 (10.4)	65.3 (10.8)	
23-49	87 (11.4)	23 (12.4)	0.2	78 (11.5)	13 (8.8)	0.001
50-59	216 (28.3)	42 (22.6)		196 (28.8)	26 (17.7)	
60-69	255 (33.5)	57 (30.6)		230 (33.8)	48 (32.7)	
70-89	204 (26.8)	63 (33.9)		177 (26.0)	60 (40.8)	
Type of resistance, PRROC						
Primary platinum-refractory	56 (7.3)	9 (4.8)	0.1	45 (6.6)	6 (4.1)	0.6
Primary platinum-resistant	181 (23.8)	54 (29.0)		171 (25.1)	32 (21.8)	
Secondary platinum-refractory	71 (9.3)	19 (10.2)		61 (9.0)	14 (9.5)	
Secondary platinum-resistant	138 (18.1)	42 (22.6)		129 (18.9)	27 (18.4)	
Potentially platinum-sensitive≥3[a]	316 (41.5)	62 (33.3)		275 (40.4)	68 (46.3)	
ECOG performance status						
0	269 (35.3)	60 (32.3)	0.3	249 (36.6))	44 (29.9)	0.4
1	416 (54.6)	101 (54.3)		372 (54.6)	88 (59.9)	
2	70 (9.2)	25 (13.4)		57 (8.4)	15 (10.2)	
3	7 (0.9)	0		3 (0.4)	0	
Lines of previous treatment for ovarian cancer						
1	144 (18.9)	41 (22.4)	0.7	132 (19.4)	29 (19.7)	0.5
2	291 (38.2)	65 (34.5)		247 (36.3)	62 (42.2)	
3	171 (22.4)	40 (21.5)		158 (23.2)	31 (21.1)	
≥4 (maximum 10)	156 (20.5)	40 (21.5)		144 (21.1)	25 (17.0)	
Response to most recent line						
Complete response	98 (12.9)	21 (11.3)	0.9	95 (14.0)	18 (12.2)	0.4
Progressive disease	309 (40.6)	72 (38.7)		269 (39.5)	54 (36.7)	
Partial response	201 (26.4)	54 (29.0)		190 (27.9)	36 (24.5)	
Stable disease	129 (16.9)	29 (15.6)		111 (16.3)	31 (21.1)	
Unknown	23 (3.0)	6 (3.2)		15 (2.2)	6 (4.1)	

Table 2. Results from exploratory factory analysis (EFA) and hierarchical cluster analysis (HCA) at baseline (n= 762) and during treatment (n=681)

		Baseline (i.e. before next-line of chemotherapy)					During treatment				
MOST index	MOST items	EFA 3 factor	EFA 4 factor	EFA 5 factor	HCA threshold <10[c]	HCA threshold <15[d]	EFA 3 factor	EFA 4 factor	EFA 5 factor	HCA threshold <10	HCA threshold <15
MOST-Abdo	Abdominal pain, discomfort and/or cramps	A[a]	D	D	-	D	A	A	D	D	A
MOST-Abdo	Abdominal swelling, bloating and/or fullness	A	D	D	-	D	A	A	D	D	A
MOST-Chemo	Altered sense of taste	A	A	-	-	-	-	D	E	-	A
MOST-Chemo	Sore mouth or throat	-[b]	-	E	B	B	B	D	E	E	A
MOST-Chemo	Hair loss	-	-	-	-	-	-	-	-	-	-
MOST-Chemo	Skin rash	-	-	-	B	B	B	-	-	E	A
MOST-Chemo	Numbness or pins and needles	B	B	B	-	-	B	B	B	B	B
MOST-Chemo	Sore hands and feet	B	B	B	-	-	B	B	B	B	B
MOST-DorT	Bladder problems	-	-	-	-	-	-	-	-	E	A
MOST-DorT	Constipation	A	-	-	-	-	A	A	-	-	A
MOST-DorT	Diarrhoea	A	-	E	-	-	-	-	-	-	A
MOST-DorT	Difficulty swallowing	-	-	-	B	B	B	D	E	E	A
MOST-DorT	Fatigue (tiredness)	A	D	D	-	-	A	A	-	-	-
MOST-DorT	Indigestion	A	A	A	-	A	A	A	D	-	A
MOST-DorT	Nausea	A	A	A	A	A	A	A	A	A	A
MOST-DorT	Shortness of breath	-	-	-	-	-	-	-	-	-	A
MOST-DorT	Trouble eating	A	A	A	-	-	A	A	-	-	A
MOST-DorT	Trouble sleeping	-	-	-	-	-	-	-	-	-	-
MOST-DorT	Vomiting	A	A	A	A	A	A	A	A	A	A
MOST-Psych	Anxiety (feeling worried)	C	C	C	-	C	C	C	C	C	A
MOST-Psych	Depression (feeling sad)	C	C	C	-	C	C	C	C	C	A
MOST-T35 Q31	Trouble concentrating	C	C	C	-	-	C	C	C	-	A

[a]Capital letters indicate symptom clusters. For EFA analyses, the criterion for inclusion in a symptom cluster was a factor loading >.40 on the same factor. For HCA analyses symptom cluster are indicated by the distance at which branches join in the dendrogram.

[b]Dash indicates the symptom did not meet the analysis criterion for inclusion in a cluster.

[c]HCA lower threshold (rescaled distance <10) criterion for inclusion in a cluster.

[d]HCA higher threshold (rescaled distance (<15) criterion for inclusion in a cluster.

Figure 1. Dendrogram illustrating the results of the hierarchical cluster analysis "baseline" (i.e. before first cycle of next-line of chemotherapy; n = 762). *The distance at which branches join indicates similarity (shorter branch represents greater similarity).*

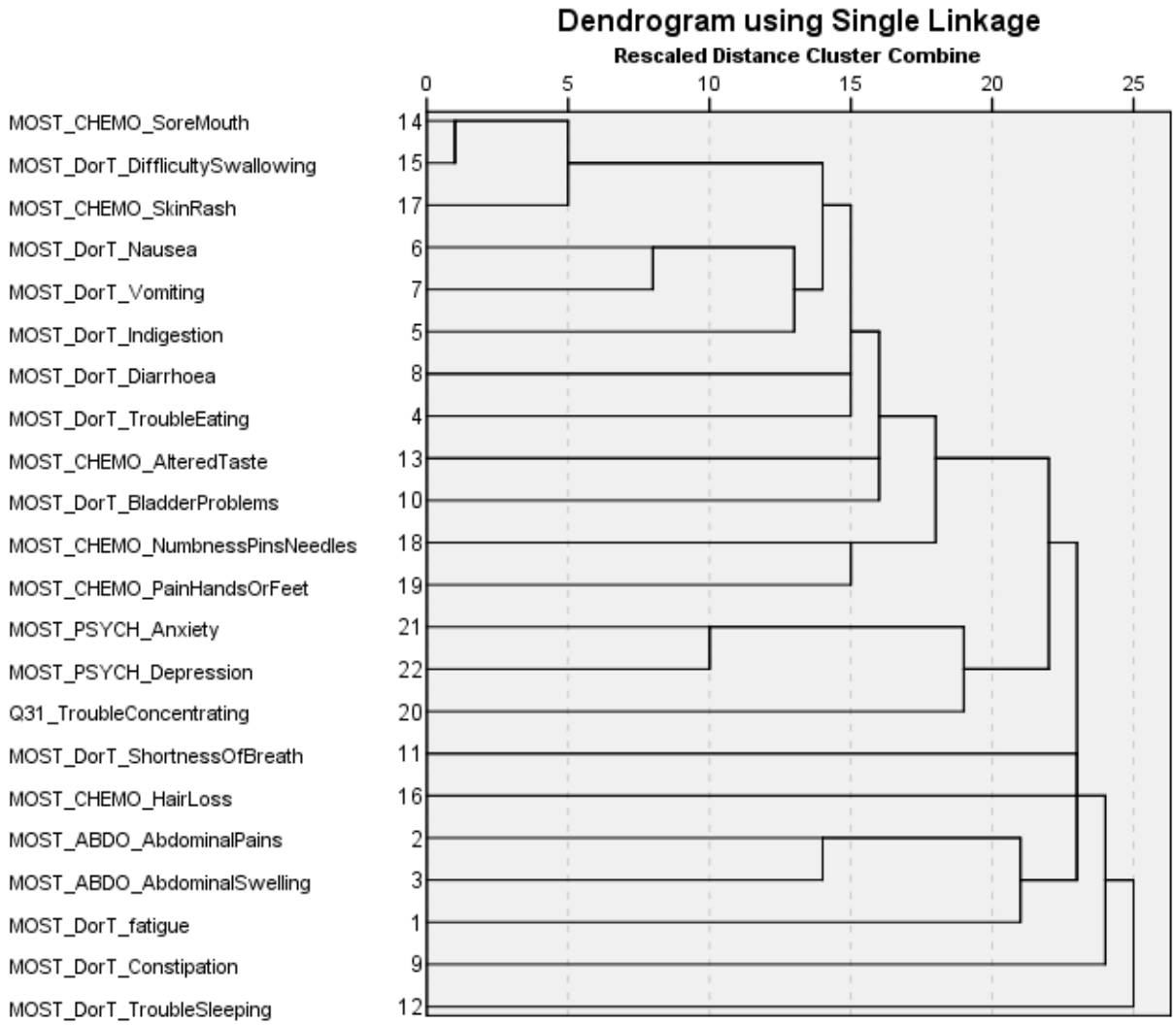

Figure 2. Dendrogram illustrating the results of the hierarchical cluster analysis during treatment (n = 681). *The distance at which branches join indicates similarity (shorter branch represents greater similarity).*

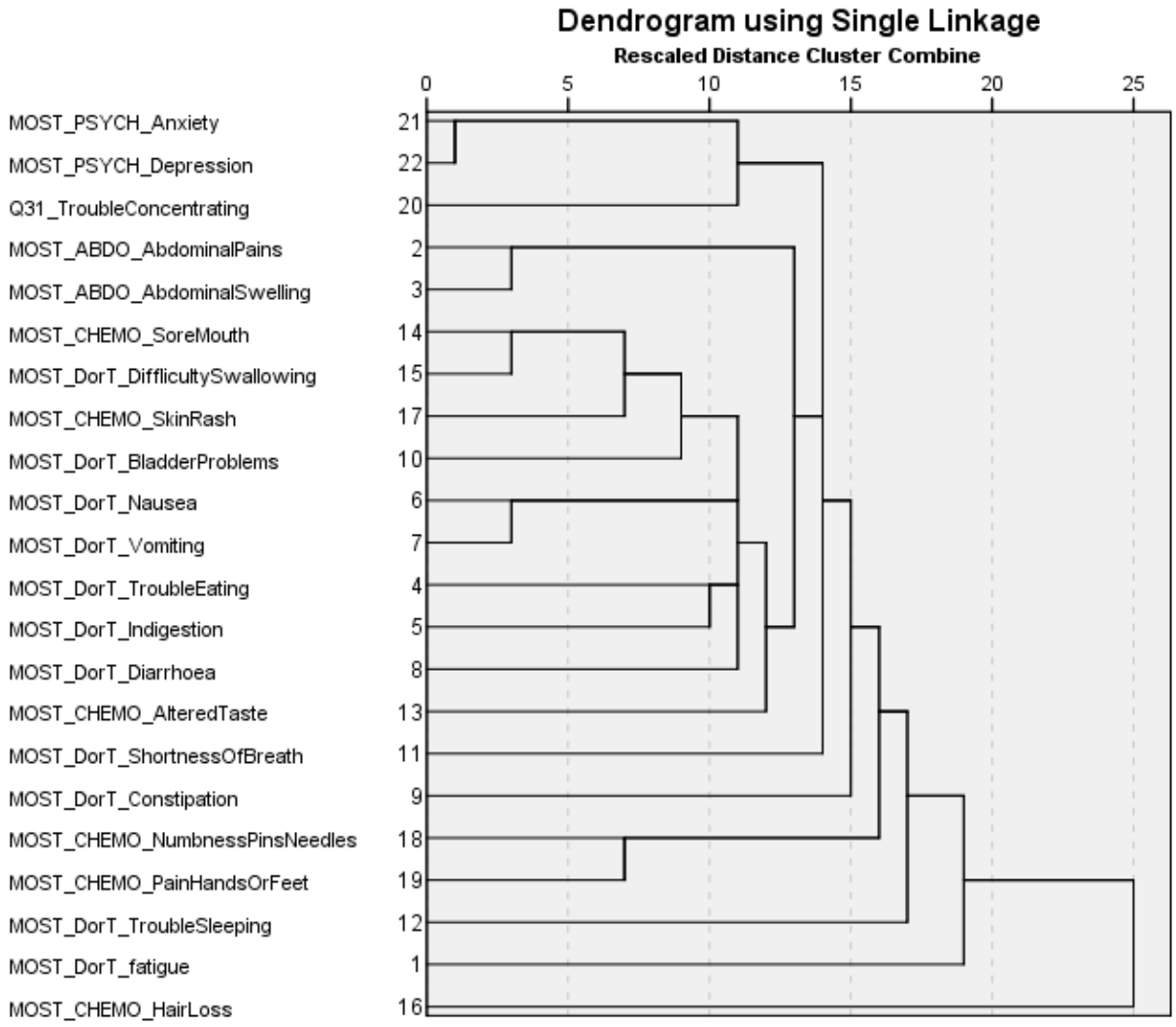

Table 3. Results from path models examining associations between MOST symptom indexes and HRQL domains at "baseline" (i.e. before next-line of chemotherapy; n = 762)

	HRQL Domains							
Predictors	QLQ-C30 Physical	QLQ-C30 Social	QLQ-C30 Role	QLQ-OV28 Body image	QLQ-OV28 Attitude to disease/ treatment	QLQ-OV28 Sexuality	QLQ-C30 Overall health	QLQ-C30 Overall quality of life
MOST-Abdo	-.001	-.10[a]	-.22[b]	.18[b]	.15[b]	.07	-.12[b]	-.01
MOST-DorT	-.41[b]	-.30[b]	-.30[b]	.03	-.07	-.02	-.21[b]	.02
MOST-Chemo	-.03	-.003	-.07	.10[a]	.09[a]	-.07	-.04	-.03
MOST-NTx	-.12[b]	-.04	-.004	-.02	.04	.03	-.01	.04
MOST-Psych	-.06	-.18[b]	-.11[b]	.30[b]	.53[b]	-.16[b]	-.06	-.07[b]
QLQ-C30 Physical	-	-	-	-	-	-	.13[b]	.05[a]
QLQ-C30 Social	-	-	-	-	-	-	.09[a]	.11[b]
QLQ-C30 Role	-	-	-	-	-	-	.26[b]	.03
QLQ-OV28 Body image	-	-	-	-	-	-	-.03	.01
QLQ-OV28 Attitude	-	-	-	-	-	-	-.08[a]	-.08[b]
QLQ-OV28 Sexuality	-	-	-	-	-	-	.02	.04[a]
QLQ-C30 Overall health	-	-	-	-	-	-	-	.69[b]

For all MOST indexes, a higher score means worse symptoms. For all functioning, health and quality of life domains, a higher score means better functioning, health or quality of life. For body image and attitude to disease and treatment, higher scores indicate worse problems in these domains.

Model fit: RMSEA=0.12, CFI=.96, SRMR=.05; All coefficients are standardized.

Abdo, abdominal; Chemo, chemotherapy; DorT, disease and or treatment, NTx, Neurotoxicity; Psych, psychological.

[a] $p < 0.05$.

[b] $p < 0.01$.

Table 4. Results from path models examining associations between MOST symptom indexes and HRQL domains during treatment ($n = 681$)

	HRQL Domains							
Predictors	QLQ-C30 Physical	QLQ-C30 Social	QLQ-C30 Role	QLQ-OV28 Body image	QLQ-OV28 Attitude to disease/ treatment	QLQ-OV28 Sexuality	QLQ-C30 Overall health	QLQ-C30 Overall quality of life
MOST-Abdo	-.02	-.06	-.08	.09	.02	-.05	-.11[b]	.01
MOST-DorT	-.47[b]	-.31[b]	-.43[b]	.04	.13[b]	-.05	-.17[b]	.02
MOST-Chemo	.02	.01	-.02	.07	-.03	.05	.06	-.03
MOST-NTx	-.07	-.002	-.01	.04	.04	-.03	-.03	.03
MOST-Psych	-.12[b]	-.26[b]	-.10[a]	.34[b]	.56[b]	-.11[a]	-.09[a]	-.07
QLQ-C30 Physical	-	-	-	-	-	-	.08	.05
QLQ-C30 Social	-	-	-	-	-	-	.03	.03
QLQ-C30 Role	-	-	-	-	-	-	.31[b]	.09
QLQ-OV28 Body image	-	-	-	-	-	-	-.09[a]	.04
QLQ-OV28 Attitude	-	-	-	-	-	-	-.09[a]	-.05
QLQ-OV28 Sexuality	-	-	-	-	-	-	.05	.07
QLQ-C30 Overall health	-	-	-	-	-	-	-	.75[a]

For all MOST indexes, a higher score means worse symptoms. For all functioning, health and quality of life domains, a higher score means better functioning, health or quality of life. For body image and attitude to disease and treatment, higher scores indicate worse problems in these domains.
Model fit: RMSEA=0.15, CFI=.94, SRMR=.05; All coefficients are standardized.
Abdo, abdominal; Chemo, chemotherapy; DorT, disease and or treatment, NTx, Neurotoxicity; Psych, psychological.
[a]$p < 0.05$.
[b]$p < 0.01$.