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An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer

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Abstract

This study defines the psychometric properties of the European Organisation for Research and Treatment of Cancer (EORTC) quality of life (QOL) questionnaire designed to measure the QOL of patients with ovarian cancer. The ovarian cancer module (EORTC QLQ-OV28) was developed to supplement the EORTC QLQ-C30. The core questionnaire and the QLQ-OV28 were prospectively administered to 368 ovarian cancer patients after they had been treated with radical or debulking surgery followed by chemotherapy. The QLQ-OV28 module assesses abdominal/gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side-effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment and sexual functioning. Questionnaires were well accepted by patients, baseline compliance rates were 86%, 72% provided a second assessment, less than 3% of the items had missing data. Multi-trait scaling analyses confirmed the hypothesised scales. All hypothesised scales exhibited good psychometric properties. These results support the clinical and psychometric validity of the EORTC QLQ-OV28 module as a supplement to the EORTC QLQ-C30.

Keywords: Quality of life assessment; Ovarian cancer; EORTC; Questionnaire

1. Introduction

The standard approach for treating patients with ovarian cancer is surgery followed by chemotherapy. For women with early stage disease, surgery is potentially curative and 5-year survival rates are around 70% [1]. However, they are at a high risk of recurrence and may therefore be advised to accept adjuvant chemotherapy. Most patients present with more advanced disease, with 5-year survival rates around 30%. Over the past 20 years, different combinations of cytostatic drugs including different doses and modes of delivery have been tried to optimise treatment gain and reduce toxicity. The combination of platinum-paclitaxel is internationally accepted as first-line management for advanced ovarian cancer following the results of two randomised trials [2,3], consensus statements from the United States (US) [4] and the United Kingdom (UK) [5,6] and an international consensus meeting [7]. High response rates to first-line treatment can now be achieved, but still at a cost in terms of unpleasant side-effects. There is now considerable research activity

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involved in order to try to optimise first and second-line treatments for patients with advanced or recurrent disease. Quality of life (QOL) outcomes are of particular relevance in evaluating palliative treatments [8,9]. Most patients with advanced disease will relapse, often with disease resistant to the first-line agents they have received. With a growing emphasis on the need for evidence-based practice and for involving patients in treatment decision-making, patient-reported QOL outcomes have become important and should be more frequently assessed in ovarian cancer trials. The measure used should cover the predominant disease- and treatment-related issues.

The QLQ-C30 core questionnaire—developed by the European Organisation for Research and Treatment of Cancer (EORTC) QOL Group—is a psychometrically robust, cross-culturally accepted questionnaire, which was designed to be applicable to a broad spectrum of cancer patients [10]. It has been validated for ovarian cancer patients [11] and recommended by independent reviewers for use in clinical and research settings [12]. The EORTC QLQ-C30 measure (version 3.0) consists of five function scales: physical, role, emotional, cognitive and social; three symptom scales: fatigue, nausea/vomiting and pain; six single-item scales: dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact; and also a global QOL scale. The EORTC Quality of Life Group measurement strategy is to supplement the core EORTC QLQ-C30 with disease- and/or treatment-specific modules to address additional issues.

The EORTC QLQ-OV28 module contains issues of relevance to the QOL of patients with ovarian cancer and was developed in a multicultural setting. The detailed development process of the module has been described elsewhere in Ref. [13]. The module has been translated into 14 languages (English, Croatian, Danish, Dutch, French, German, Italian, Portuguese, Spanish, Swedish, Taiwan-Chinese, Finnish, Norwegian and Polish) according to the EORTC QOL Group guidelines [14]. Although a shorter version of the module has been previously used in a single country phase III trial, in Scotland (SCOTROC) [15], the clinical and psychometric properties of the entire scale have not been formally tested. The aim of this international field study was to confirm the hypothesised scale structure and to determine the reliability, validity and cross-cultural applicability of the EORTC QLQ-OV28.

2. Patients and methods

The prospective study (EORTC protocol 15982) was activated in January 1999 and closed to patient recruitment in July 2001—was co-ordinated at the Quality of Life Unit at the EORTC Data Centre in Brussels, Belgium. Patients were eligible if they had a diagnosis of epithelial ovarian cancer, expected survival time of at least 3 months, and provided written consent to participate. Exclusion criteria were: concurrent malignancies, inability to understand and complete the questionnaire, or participation in another QOL study interfering with this protocol. There were no limitations with regard to age or performance status. Local or national ethical committee approvals were obtained. A total of 368 subjects were prospectively registered into the study and assigned to four groups: Group 1 consisted of patients who had radical or debulking surgery and received first-line platinum-based chemotherapy. Group 2 included patients who had radical or debulking surgery and had completed six courses of platinum-based chemotherapy. Group 3 consisted of patients who had achieved a complete response to first-line treatment and showed no evidence of disease (NED). They had not received anti-cancer treatment in the past three months. Group 4 included patients previously treated for ovarian cancer and who presented with recurrence of disease, to be treated with second-line chemotherapy.

3. Data collection

QOL assessments were conducted at various time points: Patients in Group 1 were asked to complete the questionnaire twice: prior to the start of the first cycle of chemotherapy and on the day of the fourth cycle of chemotherapy. Patients in Group 2 completed the questionnaire, at their first visit to the clinic after treatment (within 8 weeks of the sixth cycle of chemotherapy). Patients in Group 3 completed the questionnaire twice, the first time at a routine follow-up visit to the clinic and the second time at home within 3 days. They were asked to return the second questionnaire by post. Patients in Group 4 completed the questionnaire prior to the start of the first cycle of the second-line chemotherapy and the first day of the fourth cycle of chemotherapy. Patients with QOL assessments outside of this time frame were excluded from the data analyses. At all time points, the EORTC QLQ-C30 (version 3.0), the QLQ-OV28 and a debriefing questionnaire were administered. Compliance and general aspects of this study were monitored using standard EORTC procedures and reviewed every 6 months at QLG bi-annual meetings.

The newly developed QLQ-OV28 module contains 28 items in a similar layout and response format to the QLQ-C30. On clinical grounds, the hypothesised scale structure was as follows:

1. abdominal/gastrointestinal symptoms (GI)—items 31–37
2. peripheral neuropathy (PN)—items 41–43

3. other chemotherapy side-effects (CH)—items 38–40, 44–47
4. hormonal/menopausal symptoms (HM)—items 48, 49
5. body image (BI)—items 50, 51
6. attitude to disease and treatment (AT)—items 52–54
7. sexual functioning (SF)—items 55–58.

4. Statistical analysis

It was considered important to include data from patients likely to experience side-effects of chemotherapy in the assessment of the validity of the scale. Therefore, data regarding the second assessment from groups 1 and 4 and the single assessment of group 2 were primarily used in the analysis. This population will be referred to as the 'on-treatment population'. In total, this provided us with a limited number of patients ($N=154$). However, the analysis was repeated using baseline data from groups 1 and 4 and on data from the first assessment in group 3 ($N=214$) referred to as the 'off-treatment population'. In total, 311 patients provided at least one evaluable observation. Descriptive statistics were calculated for the raw scores on each item (QLQ-OV28 only), as well as for the hypothesised scales (for both QLQ-C30 and OV28), by group and assessment.

4.1. Discriminant validity

Item convergent validity for each scale was assessed using the correlation between each item and its own scale corrected for overlap. These correlation values were then compared with the correlation of each item with other scales in order to support discriminant validity. A scaling success for an item was obtained when the correlation between an item and its own scale was significantly higher than its correlation with any other scale (as assessed by a difference greater than twice the approximate standard error of the correlation).

4.2. Reliability

Internal consistency was calculated using Cronbach's alpha coefficient for each scale. In addition, test-retest properties of the scales were assessed using the intra-class correlation coefficient.

4.3. Responsiveness

Assessment of responsiveness of the scales to treatment was done by comparison of pre-treatment versus on-treatment assessment in groups 1 and 4. Because of the non-normality of the data, non-parametric testing was used for that purpose.

4.4. Clinical validity

Known-group comparisons were carried out using clinical information such as the Karnofsky Performance Status score, absence/presence of ascites, Common Toxicity Criteria (CTC) and the International Federation of Gynecology and Obstetrics (FIGO) staging. Patients with primary disease versus patients with NED (group 1 vs. group 3) and patients with recurrent disease versus patients with NED (group 4 vs. group 3) were also compared. Those comparisons were statistically tested using non-parametric methods (Wilcoxon 2-sample and Kruskal-Wallis tests). All tests were performed using statistical analysis software (SAS).

5. Results

5.1. Patient characteristics

A total of 368 ovarian cancer patients from six different countries were entered into the study. 57 patients were excluded, because the timing of the QOL assessment was outside of the specified time window of the study or patients did not return the questionnaires by post. Sociodemographic and clinical characteristics are shown in Table 1. Patients had different stages of ovarian cancer. More than half of the study participants were diagnosed with advanced stages of disease (FIGO stages III and IV).

5.2. Compliance rates

Patient compliance varied from 88% (baseline assessment) to 72% (follow-up assessment). Out of 368 patients, 316 (86%) fulfilled baseline compliance criteria (i.e. QOL questionnaires were filled in before the start of chemotherapy). One hundred and ninety-four (72%) of the 270 patients, likely to provide a second assessment, did so. Item compliance for each time point was assessed amongst patients who filled in a form at that assessment. All items except the conditional items 39, 57, 58 (upset regarding hair loss, enjoyment of sex, dry vagina) exhibited good compliance with less than 3% of missing values. Missing values for sexuality items ranged from 4.2 up to 25.8%. Most patients (76%) completed the QLQ-C30 and the OV28 in less than 15 min, and 72% did not require any help. Whenever help was required, it was mostly in order to read the items. Most patients (87%) found that the questions were clear and easy to understand. Only 8% reported that the sexuality items were upsetting.

6. Scale construction

6.1. Summary statistics and distribution of items

The scale scores were standardised to a 0–100 range and missing items were replaced using a simple imputation as in other EORTC questionnaires [16]. Missing values were replaced by the mean of the other items in the scale if at least half of the data were present for that scale; otherwise the scale value was regarded as missing. The distribution of all the items and scales are presented in Table 2. The distribution of most items was skewed towards a lower response to the items. The summary statistics for the raw questionnaire data showed that the conditional item 39 (upset about hair loss) was omitted by most patients. Items 57 (enjoyment of sex) and item 58 (dry vagina) also showed a low prevalence.

6.2. Internal consistency, item convergent and discriminant validity

Results of the multi-trait/multi-item analyses are presented in Table 3. The postulated scale structure was analysed for scaling errors using tests for item convergent and divergent validity. Internal consistency was high in all scales (Cronbach's alpha >0.70) except for the body image scale in the baseline/off-treatment data-set (Cronbach's alpha $=0.58$). All scales, except the "Other chemotherapy side-effect" scale, showed good convergence since all item-own scale correlations were higher than 0.4. There were no scaling errors of the hypothesised scales except for the "Other chemotherapy side-effect" scale, which appeared to be a fairly heterogeneous aggregation of items. The analysis was repeated on the baseline/off-treatment assessment data-set. The only difference was that item 43 ('weakness') had a higher correlation with the "Other chemotherapy side-effect" scale than with its own scale, although this was not statistically significant.

Table 1
Baseline socio-demographic and clinical information

	N (%)
Age (years)	
⩽50	91 (25)
51–60	104 (28)
61–70	112 (30)
71–80	61 (17)
Co-habitation	
Living alone	75 (20)
Living with family	267 (73)
Living with others	26 (7)
Marital status	
Single	36 (10)
Married or partner	258 (70)
Separated/divorced	74 (20)
Highest level of education[a]	
Less than school	22 (6)
Compulsory school	219 (60)
Post compulsory school	103 (28)
University level	23 (6)
Employment	
Full time	65 (18)
Part time	46 (13)
Homemaker	99 (27)
Unemployed	12 (3)
Retired	135 (31)
Other	11 (3)
Stage of disease	
FIGO I	103 (31)
FIGO II	34 (10)
FIGO III	172 (51)
FIGO IV	28 (8)

FIGO, the International Federation of Gynecology and Obstetrics.
[a] Some data are missing.

Table 2
Summary statistics for the OV28 items

Items	*N*[a]	Mean	S.D.	Median
31. Abdominal pain	503	1.53	0.78	1.00
32. Feeling bloated	501	1.65	0.86	1.00
33. Clothes too tight	502	1.50	0.82	1.00
34. Changed bowl habit	502	1.73	0.95	1.00
35. Flatulence	502	1.85	1.00	2.00
36. Fullness when eating	500	1.49	0.81	1.00
37. Indigestion/heartburn	503	1.47	0.78	1.00
38. Hair loss	492	1.68	1.07	1.00
39. Upset regarding hair loss	156	2.36	1.15	2.00
40. Taste change	490	1.30	0.66	1.00
41. Tingling hands/feet	499	1.65	0.96	1.00
42. Numbness in fingers/toes	500	1.59	0.95	1.00
43. Weakness in arms/legs	499	1.61	0.85	1.00
44. Muscle aches/pains	503	1.77	0.92	2.00
45. Hearing problem	500	1.36	0.71	1.00
46. Urinary frequency	500	1.74	0.90	1.00
47. Skin problem	501	1.54	0.82	1.00
48. Hot flushes	501	1.80	0.97	1.00
49. Night sweats	503	1.73	0.95	1.00
50. Feel less attractive	499	1.68	0.95	1.00
51. Dissatisfied with body	498	1.79	0.97	1.00
52. Disease burden	492	2.38	1.01	2.00
53. Treatment burden	484	2.08	1.05	2.00
54. Worry about future	497	2.44	1.09	2.00
55. Interest in sex	482	1.56	0.81	1.00
56. Sexual activity	473	1.56	0.80	1.00
57. Enjoyment of sex	165	2.70	0.84	3.00
58. Dry vagina	165	1.98	0.97	2.00

S.D., standard deviation.
[a] Number of responses.

6.3. Test-retest reliability

Test–retest reliability of the scales was assessed using the Intra-Class Correlation coefficient (ICC) calculated on the values from group 3. ICC values ranged from 0.74 to 0.94 showing good repeatability of the scales (Table 4).

6.4. Relationship between core questionnaire and ovarian module

Most scales in the QLQ-OV28 module were weakly correlated with the QLQ-C30 scales. However, the ovarian abdominal/gastrointestinal symptom scale (GI) appeared to be moderately correlated with QLQ-C30 social functioning scale, pain scale and the nausea/vomiting scale; the ovarian attitude to disease and treatment scale (AT) was moderately correlated with QLQ-C30 emotional functioning scale and ovarian "Other chemotherapy side-effects" scale (CH) with the QLQ-C30 fatigue scale.

6.5. Responsiveness to treatment

Differences between pre-chemotherapy and on-chemotherapy assessments in groups 1 and 4 were evaluated for items and scales of the QLQ-OV28, as well as for the QLQ-C30 scales. In general, the same tendency is observable in both groups and they were therefore analysed together in order to increase the power of the test. Since the scores are generally not normally distributed, a non-parametric test for paired data (Wilcoxon signed rank test) was used to formally test the response of each scale to treatment (Table 5). All scales except body image and hormonal/menopausal symptoms showed significant differences between the two assessments. However, these results have to be interpreted with caution given the fairly limited number of observations.

6.6. Clinical validity

The method of known-group comparison was used to explore to what extent the QLQ-C30 and the OV28 are

Table 3
Internal consistency, item convergent and discriminant validity

Scale	On-treatment data-set				Off-treatment data-set			
	Cronbach's alpha	Item—own scale correlation[a]	Item—other scale correlation[b]	Scaling errors	Cronbach's alpha	Item—own scale correlation	Item—other scale correlation[b]	Scaling errors
Abdominal/gastrointestinal symptoms (GI) Items 31–37	0.86	0.45–0.68	0.05–0.48	0/42	0.84	0.51–0.77	0.03–0.50	0/42
Peripheral neuropathy (PN) Items 41–43	0.77	0.48–0.76	0.06–0.46	0/18	0.83	0.56–0.79	0.01–0.61	1/18
Other chemotherapy side-effects (CH) Items 38–40 and 44–47	0.79	0.20–0.51	0.01–0.37	5/42	0.77	0.35–0.78	0.05–0.59	2/42
Hormonal/menopausal symptoms (HM) Items 48, 49	0.80	0.64	0.02–0.34	0/12	0.83	0.72	0.05–0.43	0/12
Body image (BI) Items 50, 51	0.79	0.63	0.02–0.41	0/12	0.58	0.41	0.07–0.43	0/12
Attitude to disease and treatment (AT) Items 52–54	0.87	0.53–0.71	0.03–0.45	0/18	0.78	0.55–0.72	0.06–0.48	0/18
Sexual function (SE) Items 55–58	0.78	0.49–0.87	0.01–0.23	0/24	0.90	0.52–0.88	0.01–0.22	0/24

[a] Corrected for overlap.
[b] The opposite value is displayed for negative correlations.

Table 4
Test–retest of EORTC QLQ-OV28 scales

QLQ-OV28-scales	Between subject S.D.	Within-subject S.D.	ICC[a]
Abdominal/gastrointestinal	20.42	6.33	0.91
Peripheral neuropathy	25.51	9.58	0.88
Other chemotherapy side–effects	16.94	7.27	0.84
Hormonal/menopausal symptoms	31.09	7.68	0.94
Body image	23.84	11.36	0.82
Attitude to disease and treatment	28.42	12.39	0.84
Sexual function	13.82	8.20	0.74

[a] ICC = intra-class correlation coefficient.

Table 5
Responsiveness of scales from EORTC QLQ-OV28

QLQ-OV28-scales	*N*	Mean	Median	*P* value
Abdominal/gastrointestinal	59	−7.4	−4.8	0.0054
Peripheral neuropathy	59	8.7	0.0	0.0248
Other chemotherapy side-effects	59	15.3	19.0	0.0001
Hormonal/menopausal symptoms	59	0.6	0.0	0.5320
Body image	58	−1.1	0.0	0.6733
Attitude to disease and treatment	57	−7.5	0.0	0.0475
Sexual function	53	4.1	0.0	0.0736

able to discriminate between subgroups of patients differing in terms of their clinical status. The KPS score of patients from groups 1, 2 and 4 was considered as a categorical variable. Non-parametric ANOVA (Kruskal–Wallis test) was applied to the QLQ-OV28 scales to test for differences in the KPS groups thus formed. In addition, patients from groups 1 and 4 whose KPS scores changed between baseline and on-treatment assessments were identified and the scale scores were compared between the three groups. Patients at baseline were also grouped according to whether they had clinically significant ascites or not. The two groups thus formed were compared. There was no clear discrimination between the two groups apart from Sexual functioning (SF). Similarly, the OV28 scales were compared across stages of disease according to the patient's FIGO staging. The scales appear to discriminate best when comparing patients with first presentation of disease to patients with a recurrence.

7. Discussion

The goal of new approaches to ovarian cancer treatment is to improve the quality, as well as the duration, of patients' lives. The need to assess outcomes in terms of patients' experience is increasingly recognised. Generic QOL measures do not adequately capture specific disease- and/or treatment-related issues which affect the QOL of women treated for ovarian cancer in international clinical trials. For this purpose, a questionnaire was developed to supplement the widely used EORTC QLQ-C30 for use in clinical trials. In this international field study, the EORTC QLQ-C30 and the QLQ-OV28 module was tested in a sample of 368 women with ovarian cancer.

The module proved to be acceptable to a heterogeneous sample of patients, most of whom completed the EORTC QLQ-C30 and the ovarian cancer module in less than 15 min. The scale structure of the QLQ-OV28 was examined in various subpopulations (on-treatment and off-treatment). Statistical analyses confirmed six subscales (abdominal/gastrointestinal, peripheral neuropathy, other chemotherapy side-effects, hormonal/menopausal symptoms, body image and sexual functioning, attitude to disease and treatment).

In a Scottish randomised ovarian cancer trial, the module was used without the sexual function items. In the first phase of module development, items pertaining to sexual function had lower ratings for relevance to patients than the other items included. The burden of these questions is minimal since only two items (libido and extent of sexual activity) are asked of all patients. The remaining two questions are asked only to those who are sexually active. These items may be more appropriate to some studies than to others. They were included at the end of the module so that they could be omitted without interfering with the order in which the other items are presented.

Based on the data of the Scottish trial, a first scaling analysis was conducted on the first 24 items of the module without the sexual functioning items [13]. The scale structure differed slightly from the hypothesised one and from the corresponding internal consistency. The "Other chemotherapy side-effect" scale was limited to four items 44–47 (muscle aches/pains, hearing problems, urinary frequency and skin problems). Item 43 (weakness) was removed from the peripheral neuropathy scale; item 37 (indigestion/heartburn) was removed from abdominal/gastrointestinal scale and kept as a single item as well as items 38–43 (hair loss, upset regarding hair loss, taste change, tingling hands/feet, numbness in fingers/toes, weakness in arms/legs). However, in this field study the original scale structure was confirmed incorporating all chemotherapy-related items (38–40, 44–47) in one scale. These findings can be used in two ways: as a subscale representing cumulative treatment effects, or as single items as suggested by Cull and colleagues [13]. The issues covered are clinically distinct and it may be more informative to clinicians to use the items individually. In spite of the different distribution of responses in the two data-sets, the scale structure derived from the on-treatment data-set showed equally good properties when applied to the off-treatment data.

While the results show this is a robust instrument, some caution is warranted. Test–retest was assessed in patients who were disease-free when they assessed their QOL and we can only speculate that these results will extrapolate to patients under active treatment. Known-group comparisons are not as convincing as one would expect. It must be highlighted at this point that classical psychometric properties are not so relevant in the presence of symptom items which are likely to be causal variables of QOL as opposed to effect indicators. The crucial feature is content validity (or breadth of coverage) i.e. we need to make sure that all potential symptoms influencing QOL are included in the questionnaire. Based on psychometric grounds, the questionnaire and its hypothesised scales can be recommended for use in

ovarian cancer patients. These results might be attributable to a lack of power in comparing those groups (sample size is limited) or might simply reflect the fact that the OV28 scales are measuring something different from the clinical endpoints.

In summary, the EORTC QLQ-OV28 has been developed according to the formal guidelines of the EORTC Quality of Life Group. It is intended to be used in its entirety including all seven subscales. The module should be scored according to EORTC conventions i.e. the average of the items that contribute to each scale is taken as the raw score. Raw scores are linearly transformed to a 0–100 scale in which a high score represents a higher level of problems. The EORTC QLQ-OV28 has undergone prospective psychometric testing in a multicultural setting. The results confirmed the hypothesised scale structure, reliability and validity of the module. Based on psychometric grounds, the QLQ-OV28 module can be recommended for assessing the QOL of ovarian cancer patients in clinical trials.

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