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Development of a European Organization for Research and Treatment of Cancer questionnaire module to assess the quality of life of ovarian cancer patients in clinical trials: a progress report

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Abstract

A questionnaire was developed, according to the European Organization for Research and Treatment of Cancer (EORTC) published guidelines, to supplement the EORTC quality of life questionnaire-core 30 (QLQ-C30) to assess the quality of life (QL) of women with ovarian cancer treated in clinical trials. The provisional 28-item module, OV28, assesses abdominal symptoms; peripheral neuropathy; other chemotherapy side-effects; hormonal symptoms; body image; attitude to disease and treatment; and sexual functioning. The first 24 items of the module (excluding sexual functioning) were included in a UK multicentre trial (SCOTROC). The trial data were used for preliminary scaling analysis. Two problematic items were identified. When these were treated as single items along with the 'other chemotherapy side-effects' the instrument showed excellent scale properties. Mean scale scores discriminated between trial patients pre- and on chemotherapy. This is a promising tool for assessing the QL of women with ovarian cancer. The EORTC international field study (Protocol 15982) to assess more fully the psychometric properties of the OV28 is well underway.

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

1. Introduction

The quality of life (QL) of women with ovarian cancer is likely to be significantly affected by the symptoms of the disease and the side-effects of chemotherapeutic agents used in treatment. The need to evaluate systematically the balance between the costs and benefits of treatment, including from the patient's perspective is increasingly being recognised [1,2].

For women with disease confined to the ovaries (the International Federation of Gynecology and Obstetrics (FIGO) stage I) surgery is potentially curative and 5-year survival rates are approximately 70% [3]. Women with early-stage disease, at high risk of recurrence may nonetheless be advised to accept adjuvant chemotherapy. The majority of patients present with more advanced disease. Five-year survival rates for them have until recently remained at approximately 30%. The standard approach to their management is surgery

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followed by combination chemotherapy. Clinical trial activity over the past 20 years has investigated different combinations of drugs, doses and modes of delivery to optimise treatment gain and reduce toxicity. High response rates to first-line treatment can now be achieved, but still at a cost in terms of unpleasant side-effects. The combination of platinum–paclitaxel is commonly used in first-line management following results of two randomised trials [4,5], consensus statements from the USA [6] and the UK [7,8] and an international workshop [9].

There is an ongoing research agenda in first-line treatment to which evaluation of QL outcomes is relevant. The combination of platinum–paclitaxel is now being used internationally as the control arm of ongoing multicentre randomised trials. The database of conventional outcome parameters is well established for the use of cisplatin. Carboplatin in combination with paclitaxel, preferred by many investigators, is only now being thoroughly assessed in the research setting [10,11]. Docetaxel as an alternative to paclitaxel is being assessed, specifically comparing toxicity profiles [12]. Economic issues of the cost at which treatment benefits are achieved remain pertinent. The debate could usefully be informed by comparing quality of life data as well as monetary costs [13]. The majority of patients will relapse, often with disease resistant to the first-line agents received. There is now considerable research activity involved in the effort to optimise second-line treatment for patients with advanced or recurrent disease. Quality of life outcomes are of particular relevance in evaluating these essentially palliative treatments [14,15].

Evidence from other patient groups shows that QL measures can generate useful data by which cancer treatment outcomes can be compared [16], on occasion challenging previously held clinical assumptions [17]. Few of these studies have been undertaken in treatment trials for ovarian cancer, although it has been shown that women with ovarian cancer differ markedly from clinicians in their assessment of the impact of treatment toxicity [18]. A growing body of data, including those from ovarian cancer patients, has shown that pretreatment QL measures can provide significant independent prognostic information [19,20]. With a growing emphasis on the need for evidence-based practice and for involving patients in treatment decision making, patient-reported QL outcomes should be more frequently assessed in ovarian cancer trials. The measure used should cover the salient disease- and treatment-related issues.

The 'core' QL measure developed by the EORTC QL Group — EORTC QLQ-C30 — is a psychometrically robust, cross-culturally acceptable questionnaire which was designed to be applicable to a broad spectrum of cancer patients [21]. Now in its third version and translated into 38 languages, it is widely in use in clinical trials around the world. It has been validated for use with ovarian cancer patients [22] and recommended by independent reviewers for use in that setting [23]. The EORTC strategy is to supplement the EORTC QLQ-C30 with disease- and/or treatment-specific modules to address additional issues of relevance to the QL of particular patient groups. These may include psychological issues such as attitude to treatment and generic issues not covered by the 'core' instrument (e.g. sexuality) as well as specific disease and/or treatment effects. Procedural guidelines for the development of modules have been published [24]. The process, from inception to the emergence of a measure of proven clinical sensitivity, psychometric reliability/validity and cross-cultural applicability, takes several years and can be enhanced by shared experience while the instrument is under development.

The aim of this paper is to report progress in the development of a questionnaire module designed for use with the EORTC QLQ-C30 to assess the quality of life of women with ovarian cancer in clinical trials. First, the development of the provisional questionnaire, according to the published guidelines, is briefly described. A more detailed EORTC internal report is available on request. A preliminary analysis of the scale structure has been undertaken using data from a phase III trial in the UK [12]. The results, which form the second part of this report, are presented to inform users how to score the module.

2. Patients and methods

2.1. Development of the provisional module

2.1.1. Phase 1: generation of QL issues

The aim was to identify issues for inclusion in the module. Issues had to be relevant to the quality of life of women with ovarian cancer treated in the clinical trial setting i.e. disease symptoms, treatment side-effects and QL dimensions insufficiently covered by the EORTC QLQ-C30. Literature searches of Medline and BIDS science and social science databases for 1990–1997 were conducted. A list of 50 issues was derived. The relevance of these issues was rated in five countries (Austria, Scotland, Spain, Sweden and the USA) by 19 clinicians and 13 nurses, all experienced in treating ovarian cancer. They were given the opportunity to add issues not included in the list. The revised list was administered to 82 ovarian cancer patients in the same five countries. This sample, representative of patients for whom the module was being designed, was heterogeneous with respect to FIGO staging (I–IV) and treatment stage (pretreatment, i.e. chemotherapy; on first-line or subsequent chemotherapy; off treatment). The average age was 59 years (standard deviation (S.D.) = 12). The

women rated the relevance of each issue by considering the extent to which they had experienced it and the trouble/distress it had caused them. Issues with the highest mean relevance ratings from patients, were reviewed for overlap and relevance to the clinical trial setting. Thus 26 issues were derived. Issues affecting a smaller proportion of patients but which were troublesome when they occurred, were reviewed. As a result, issues concerning peripheral neuropathy and sexual function were retained. Phase 1 resulted in 33 issues for which questionnaire items were required.

2.1.2. Phase 2: operationalisation

The aim was to generate questionnaire items for the module which were as far as possible compatible with: (a) the EORTC QLQ-C30 (in terms of response format and time-frame); (b) items of pre-existing EORTC modules; and (c) good practice in questionnaire construction [25]. The 33 issues were covered by 29 questions: 16 were adopted or adapted from the breast, colorectal and oesophageal modules and 13 new items were generated. The hypothesised structure was of seven multi-item scales: abdominal/gastrointestinal (GI) symptoms; peripheral neuropathy; other chemotherapy side-effects; hormonal symptoms; body image and attitude to disease and treatment. The four-item sexual functioning scale was added at the end so that these items could be omitted, if necessary, without disrupting the remaining structure of the module.

2.1.3. Phase 3: pre-testing

The provisional module was translated according to EORTC Translation Guidelines [26] into German (Austrian), French, Spanish and Swedish. The aim was to generate translations which were easy to understand, in language of common use and conceptually equivalent to the original. When wording was problematic, patients were offered alternative forms and asked which they preferred. The aim of pretesting is to identify and solve any problems with item construction. A new sample of 142 patients in six countries (the original five plus France) completed the EORTC QLQ-C30, the provisional module and an interview. Patients were heterogeneous with respect to disease stage and treatment status. The mean age was 58 years (S.D. = 12). The 29 items were considered according to published criteria [27], i.e. on pre-testing:prevalence $\geqslant 30\%$; mean response rating $\geqslant 1.5$; response range $\geqslant 2$. In addition, at least 1/3 specialists and 1/3 patients previously interviewed should have rated the issue a priority for inclusion in the module. Items meeting fewer than 3/5 of these criteria should be considered for deletion. One item "to what extent do you consider your treatment worthwhile?" was deleted. It did not discriminate well between patients and 6 patients found the question distressing.

2.1.4. Current status of the module

The provisional module, EORTC QLQ-OV-28, has 28 items, is copyright to the EORTC and is available on request. Translations in Danish, Dutch, French, German, Italian, Portuguese Spanish and Swedish are available. Norwegian, Chinese and Russian translations are in preparation. The module is the subject of an international field study (EORTC protocol No 15982) to confirm its reliability (including test–retest reliability), validity and responsiveness to clinical change. Results are expected in 2001. The instrument is in use in several ongoing clinical trials. A condition of its use at this stage is that data will be shared to contribute to psychometric studies and to provide reference values.

2.2. Scaling analysis

2.2.1. Patients

Scaling analysis was carried out using data from 277 women who had been enrolled in the Scottish Randomised Trial in Ovarian Cancer (SCOTROC) trial [12]. They were aged at least 18 years and had a histologically confirmed diagnosis of epithelial ovarian cancer, FIGO stage Ic–IV. Eligible patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant 2$. They were randomised to receive paclitaxel or docetaxel in addition to carboplatin as their first-line chemotherapy.

2.2.2. Available data

QL was one of four secondary endpoints of the trial. Permission had been sought and given for the sexual functioning scale to be omitted. This analysis, therefore, concerns the first 24 items of the EORTC OV-28. Data collected before the first and before the third cycles of chemotherapy were used in the analysis.

2.2.3. Statistical methods

Descriptive statistics were generated for the raw scores obtained on each item at the two assessment points. The raw scores for each domain and single item were then transformed to give a value 0–100. Evidence of item convergent validity for a scale was assessed using the proportion of items in that scale whose correlation with the scale was $\geqslant 0.40$, corrected for overlap. Support for item discriminant validity was based on comparison of the correlation of an item with its own scale compared with its correlation with other scales. Scaling successes are defined as the occasions when an item correlates more highly with its own scale (corrected for overlap) than with another [28]. Correlations were determined by Pearson's product moment coefficient. Internal consistency of multi-item scales was calculated using Cronbach's α coefficient [29]. Values of $\alpha \geqslant 0.70$ are considered acceptable for group comparisons. Factor analysis, using the maximum likelihood method with

Table 1
Descriptive statistics for cycle 1 and cycle 3 — raw scores

Item (abbreviated content)	Number responding = n	Mean[a]	Standard deviation	% prevalence[b]	Number responding = n	Mean[a]	Standard deviation	% prevalence[b]
31. Abdominal pain	275	1.98	0.81	71	275	1.51	0.67	42
32. Feeling bloated	275	1.73	0.88	50	275	1.49	0.70	38
33. Clothes too tight	274	1.54	0.86	34	273	1.35	0.67	26
34. Changed bowel habit	271	2.08	1.01	65	275	1.96	0.93	64
35. Flatulence	272	1.89	0.92	59	277	1.72	0.81	54
36. Fullness when eating	274	1.83	0.92	55	276	1.46	0.74	33
37. Indigestion/heartburn	272	1.45	0.79	30	274	1.47	0.66	39
38. Hair loss	264	1.06	0.29	5	274	3.09	0.94	95
39. Upset regarding hair loss	24	1.75	1.11	42	264	2.29	1.08	71
40. Taste change	270	1.39	0.77	24	273	2.00	1.01	60
41. Tingling hands/feet	269	1.09	0.31	8	274	1.57	0.85	38
42. Numbness	272	1.09	0.31	8	275	1.49	0.85	31
43. Weakness	270	1.47	0.68	38	274	1.69	0.80	51
44. Aches/pains	270	1.37	0.65	30	276	1.70	0.82	51
45. Hearing problems	270	1.15	0.45	12	277	1.19	0.51	14
46. Urinary frequency	266	1.95	0.94	58	275	1.99	0.88	65
47. Skin problems	268	1.38	0.69	28	273	1.66	0.76	50
48. Hot flushes	271	1.59	0.88	39	275	1.73	0.95	46
49. Night sweats	270	1.67	0.91	43	275	1.70	0.94	44
50. Feel less attractive	267	1.66	0.91	42	275	2.04	1.03	63
51. Dissatisfied with body	269	1.70	0.93	43	275	1.83	0.97	52
52. Disease burden	272	2.53	1.01	82	273	2.35	0.94	81
53. Treatment burden	239	1.93	0.99	56	273	2.14	0.87	76
54. Worry about the future	274	2.88	1.01	91	272	2.50	1.01	84

[a] Potential range of mean scores = 1–4.
[b] (No. scoring > 1)/N×100.

oblimin rotation was applied to the data to identify the underlying scale structure objectively [30]. The proposed scale structure was applied to data from cycle 1. Scale scores from data collected before cycles 1 and 3 were compared using the Student's t-test.

3. Results

Table 1 shows the summary statistics for the raw questionnaire data from each of the two treatment cycles. As expected, the conditional item (39) concerning 'upset about hair loss' was omitted by the majority of patients before cycle 1 and other items concerning chemotherapy side-effects i.e. 38 (hair loss), 40 (taste change), 41 (tingling hands/feet), 42 (numbness) and 45 (hearing problems) showed low prevalence in the data collected before cycle 1. We, therefore, elected to conduct the preliminary scaling analysis using data from before cycle 3.

On clinical grounds the hypothesised scale structure was as follows:

1. Abdominal/gastrointestinal (GI) symptoms: items 31–37;
2. Peripheral neuropathy: items 41–43;
3. Other chemotherapy side-effects: items 38–40 and items 44–47;
4. Hormonal symptoms: items 48 and 49;
5. Body image: items 50 and 51;
6. Attitude to disease and treatment: items 52–54.

The postulated scale structure was analysed for scaling errors using tests for item convergent and divergent validity. Item 37 (indigestion/heartburn) correlated more highly with 'other chemotherapy side-effects' than with the corrected abdominal/GI symptom scale. Item 43 (weakness) was problematic, correlating with four of the five other scales more highly than with the corrected peripheral neuropathy scale. All the hypothesised scales met the criterion for group comparison ($\alpha \geqslant 0.70$) with the exception of the 'other chemotherapy side-effects' ($\alpha = 0.55$). The scale structure was therefore re-analysed removing the problem items (37 and 43) from their respective scales to analyse them with 'other chemotherapy side-effects'. The results for this analysis are shown in Table 2. Scaling errors were found only among the 'other chemotherapy side-effects'. This remained the only scale with Cronbach's $\alpha < 0.70$. These questions should probably be treated as single items.

Table 2
Internal consistency and item convergent and discriminant validity (cycle 3 data): items 37 and 43 removed to other chemotherapy side-effects

Scale	Items	No. of items	Cronbach's α coefficient	Corrected item–scale correlations (range)	Item convergent validity test[a]	Item–scale correlations (range excluding own scale)	Item discriminant validity test[b]
1. Abdominal/GI symptoms	31, 32, 33, 34, 35, 36	6	0.78	0.47–0.67	6/6	0.01–0.46	30/30
2. Peripheral neuropathy	41, 42	2	0.89	0.81	2/2	0.07–0.27	10/10
3. Other chemotherapy side-effects	37, 38, 39, 40, 43, 44, 45, 46, 47	9	0.66	0.25–0.54	2/9	0.05–0.51	38/45
4. Hormonal	48, 49	2	0.87	0.77	2/2	0.08–0.38	10/10
5. Body image	50, 51	2	0.88	0.78	2/2	0.06–0.65	10/10
6. Attitude to disease/treatment	52, 53, 54	3	0.84	0.63–0.81	3/3	0.02–0.61	15/15

GI, gastrointestinal.
[a] No. of item–scale correlations $\geqslant 0.40$/total no. of correlations (corrected for overlap).
[b] No. of cases in which an item correlates more highly with its own scale (corrected for overlap) than with another scale/total no. of correlations.

Table 3
Scaling analysis for structure derived from factor analysis (cycle 3 data)

Scale	Items	No. of items	Cronbach's α coefficient	Corrected item–scale correlations (range)	Item convergent validity test[a] (items not conforming)	Item–scale correlations (range excluding own scale)	Item discriminant validity test[b]
Abdominal/GI symptoms	31, 32, 33, 34, 35, 36	6	0.78	0.47–0.67	6/6	0.01–0.40	30/30
Peripheral neuropathy	41, 42	2	0.89	0.81	2/2	0.09–0.34	10/10
Other chemotherapy side-effects	43, 44, 47	3	0.58	0.25–0.48	2/3 (47)	0.07–0.46	12/15
Hormonal	48, 49	2	0.87	0.77	2/2	0.14–0.35	10/10
Body image	39, 50, 51	3	0.79	0.48–0.73	3/3	0.06–0.61	15/15
Attitude to disease/treatment	52, 53, 54	3	0.84	0.63–0.81	3/3	0.02–0.58	15/15
Single items (not included in first 6 factors)	37, 38, 40, 45, 46						

[a] No. of item–scale correlations $\geqslant 0.40$/total no. of correlations (corrected for overlap).
[b] No. of cases in which an item correlates more highly with its own scale (corrected for overlap) than with another scale/total no. of correlations.
GI, gastrointestinal.

The data from cycle 3 were then subjected to factor analysis. The structure which emerged was very similar to the hypothesised structure. The factors were therefore labelled in the same way (Table 3).

There were two differences: (a) item 39 (hair loss) was included in the body image scale; and (b) three of the chemotherapy side-effects were grouped into a factor, leaving the remaining five as single items. The properties of the two structures (Tables 2 and 3) are not surprisingly very similar. The two-item body image scale (Table 2) has a higher α coefficient and the three-item factor 'other chemotherapy side-effects' has weak scale properties. The hypothesised scale structure as shown in Table 2 was, therefore, adopted and applied to the data from cycle 1 to test its reliability (Table 4).

Table 4
Reliability (internal consistency) of proposed scales tested on data from cycle 1

Scale	No. of items	Cronbach's α coefficient
1. Abdominal/GI symptoms	6	0.801
2. Peripheral neuropathy	2	0.708
3. Other chemotherapy side-effects	9	0.609
4. Hormonal	2	0.801
5. Body image	2	0.826
6. Attitude to disease/treatment	3	0.818

GI, gastrointestinal.

Raw scores for each of the five scales were linearly transformed to give a value in the range 0–100. Summary statistics were calculated and compared for cycles 1 and 3 (Table 5). Significant differences were found on all scales with the exception of hormonal symptoms.

4. Discussion

The goals of chemotherapy for ovarian cancer are 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 QL measures do not adequately capture specific disease- and/or treatment related issues which affect the QL of women

Table 5
Comparison of mean scale scores in cycles 1 or 2

Scale	Items	Cycle 1			Cycle 3			t for paired t test (df)	P for paired t test[b]
		SEM[a]	n	S.D.	SEM	n	S.D.		
Abdominal/GI symptoms	31–36	27.9	265	21.22	19.4	269	17.39	−6.9 (256)	<0.001
Peripheral neuropathy	41, 42	2.9	269	9.04	17.3	272	26.89	+8.9 (263)	<0.001
Hormonal	48, 49	21.0	270	1.65	23.8	273	1.79	+1.6 (265)	0.10
Body image	50, 51	22.5	267	1.73	31.3	274	1.90	+5.1 (263)	<0.001
Attitude to disease/treatment	52–54	47.4	238	1.86	44.4	272	1.66	−2.1 (232)	0.04

GI, gastrointestinal; df, degrees of freedom.
[a] Standard error of the mean (SEM) obtained by dividing standard deviation (S.D.) by square root of n.
[b] A level of <0.05 was considered significant.

treated for ovarian cancer in international clinical trials. We have developed an instrument to supplement the widely used EORTC QLQ-C30 for this purpose.

An extensive process of literature review and international consultation with specialists and patients ensured the content validity of the questionnaire. There was generally good agreement between specialists' and patients' ratings of the relevance of issues. Overall, professional staff rated the physical symptoms and side-effects as more relevant to patients' QL than did patients themselves. Where the ordering of the priority of issues for inclusion in the module was discrepant, patients' priorities were adopted.

Collaboration, among centres in the UK, northern, central and southern Europe and the US, at every stage of the module development process ensured that issues of cross-cultural relevance were appropriately addressed. Sensitivity is required in the translation of questions about bodily functions. Particular care was given to achieve wording which would be widely understood, socially acceptable and equivalent across countries. Patients were the final arbiters of the translations adopted.

The module was intended to be generally applicable to women with ovarian cancer. On pre-testing it proved acceptable to a heterogeneous sample of patients, the majority of whom completed the EORTC QLQ-C30 and the ovarian cancer module in less than 20 min. The module is intended to be used in its entirety. In 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 (regarding libido and extent of sexual activity) are asked of all patients. The remaining two questions are asked only of 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 they could be omitted without interfering with the order in which other items were presented. We have reported here scaling analyses based on the module without these items. Data from the EORTC field study will be analysed to confirm the reliability of the scale structure of the 28-item module i.e. with these items included. For some studies, the module may require to be supplemented with more specific questions for example, concerning the effect of ascites or treatment by the intra-abdominal route on patients' QL.

The original hypothesised scale structure had reasonably good properties. The revised scale structure, shown in Table 2 is even better. This is the scale structure which should, therefore, be used as the basis for scoring the module. The structure generated by factor analysis was similar, but with slightly inferior scale properties. Items covering 'other chemotherapy side-effects' could be aggregated to form an index of cumulative treatment effects, but the properties of this scale are weak. As the issues covered are clinically distinct they are best treated as single items. In spite of the different distribution of responses at the two data points, the scale structure derived from the data collected before cycle 3 showed equally good properties when applied to the pre-treatment data (cycle 1).

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 symptoms/problems. There was a highly significant difference in three of the mean scale scores obtained pre-treatment and after two cycles (before cycle 3) of chemotherapy by women in the SCOTROC trial (using the combined data from both trial arms). There was some reduction in the problems women reported in their attitude to the disease and treatment, but no significant change in hormonal symptoms (Table 5). Single items reflecting chemotherapy side-effects were not compared in this analysis. These data, conforming to clinical expectation, offer encouraging preliminary evidence of the ability of the module to detect clinical change. More detailed analyses of the psychometric properties of the full 28-item module tested in an international setting are urgently needed and will emerge from the EORTC field study.

Progress to date gives us some confidence in recommending the combination of EORTC QLQ-C30 and the

ovarian cancer module for assessing the QL of women with ovarian cancer in clinical trials in Europe. Collaboration in the use of these measures will allow speedier evaluation of the reliability and validity of the module and of any refinements which may be required, as well as facilitating cross-study comparison of QL outcomes for this patient population.

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