Quality of Life of Patients with Ovarian Cancer

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1. Introduction

1.1 Current status of ovarian cancer
Ovarian cancer is one of the leading female cancers around the world (International Agency for Research on Cancer, 2011). Up to now, there is no effective method of early detection (US Task Force of Preventive Services, 2011). When detected, the stages are usually advanced, and patients have poor prognosis and poor health-related quality of life (HRQoL). Patient-reported outcomes have been recommended as endpoints of clinical trials by the U.S. Food and Drug Administration (FDA) (2011). Therefore, besides improving survival, a better HRQoL is a major goal for the development of methods for new detection and treatments.

1.2 The impacts of the disease
Patients with ovarian cancer share general functioning and systemic problems with patients with other cancers (Cella et al., 1993; Cain et al., 1998; Base-Enquist et al., 2001; Aaronson et al., 1993). Regarding disease-specific problems, abdominal / gastrointestinal symptoms because of the space-occupying nature of the tumor and the malignant ascites from the tumor in the pelvic and abdominal cavity are most important issues (Cain et al., 1998; Base-Enquist et al., 2001; Cull et al., 2001; Greimel et al., 2003a, 2003b). The disease recurs easily. Patients may suffer repeating debulking surgeries and chemotherapies that affect their HRQoL.

1.3 The impacts of the treatments
The standard treatment of this disease is debulking (cytoreduction) surgery followed by platinum-based chemotherapy (du Bois et al., 2005), while a new approach of neoadjuvant chemotherapy followed by debulking surgery (Brisow & Chi, 2006). These treatments, no matter which comes first, can improve survival and improve HRQoL of patients by reducing tumor size and ascites, and also patients’ psychological distress. But they may also have negative impacts on HRQoL of patients because of the adverse effects of chemotherapy and surgery.

1.4 Other important aspects of HRQoL
The life-threatening nature of the illness can also cause psychological distress (Cull et al., 2001; Greimel et al., 2003a, 2003b). As all other gynecological cancers, patients with ovarian
cancer suffer from body image concerns and problems in sexual life (Cain et al., 1998; Base-Enquist et al., 2001; Cull et al., 2001; Greimel et al., 2003a, 2003b).

2. Domains of HRQoL affected by disease and treatments of ovarian cancer

2.1 Disease-related problems

2.1.1 General functioning and systemic symptoms
General functioning including physical, emotional, social, etc. (Cella et al., 1993; Aaronson et al., 1993) and ability of getting around (independence) are major issues in this category (Cain et al., 1998; Base-Enquist et al., 2001). Weight loss is also seen as a disease-related systemic symptom for advanced tumor (Cain et al., 1998; Base-Enquist et al., 2001).

2.1.2 Abdominal (gastrointestinal) symptoms
Abdominal (gastrointestinal) symptoms are major disease-related HRQoL problems of patients with ovarian cancer. These symptoms may include abdominal swelling, fullness, pain or cramps, indigestion, change of bowel habit, etc. Abdominal pain and bowel habit change can also arise from treatment (Cain et al., 1998; Base-Enquist et al., 2001; Cull et al., 2001; Greimel et al., 2003a, 2003b).

2.2 Treatment-related problems

2.2.1 Urological and gynecological symptoms
The urological or gynecological symptoms are not as common as other gynecological cancers, and they are usually caused by treatment. Urinary frequency and dry vagina are often complained of (Cull et al., 2001; Greimel et al., 2003a, 2003b).

2.2.2 Chemotherapy side effects
Chemotherapy can cause nausea and vomiting, poor appetite (Cella et al., 1993; Cain et al., 1998; Base-Enquist et al., 2001; Aaronson et al., 1993), hair loss (Cain et al., 1998; Base-Enquist et al., 2001; Cull et al., 2001; Greimel et al., 2003a, 2003b), peripheral neuropathy including numbness and weakness, other sensory change, skin problems and muscle pain (Cull et al., 2001; Greimel et al., 2003a, 2003b). Urinary frequency can also be attributed to chemotherapy (Cull et al., 2001; Greimel et al., 2003a, 2003b).

2.2.3 Termination of reproductive ability and menopausal symptoms
For women of reproductive age, both surgical treatment and chemotherapy can cause early menopause and the termination of reproductive ability (Cain et al., 1998; Base-Enquist et al., 2001). Menopausal symptoms caused by hormonal depletion, including hot flush (flash) and night sweats, are also experienced by these patients (Cull et al., 2001; Greimel et al., 2003a, 2003b).

2.3 Other important aspects in HRQoL

2.3.1 Body image and psychological problems
Like all other gynecological cancer, ovarian cancer per se and its treatment can cause body image and psychological problems. For the body image problems, patients may feel less attractive, less like a woman, dissatisfied with body or appearance, etc. (Cain et al., 1998; Base-Enquist et al., 2001; Cull et al., 2001; Greimel et al., 2003a, 2003b). For the psychological
problem, patients may have negative emotions (Cella et al., 1993; Aaronson et al., 1993), or suffer from burdens of and worries about disease or treatment (Cull et al., 2001; Greimel et al., 2003a, 2003b).

2.3.2 Sexuality
Like all other gynecological cancers, sexuality is negatively affected. Issues include interest in sex, real sexual activity and enjoyment (Cain et al., 1998; Base-Enquist et al., 2001; Cull et al., 2001; Greimel et al., 2003a, 2003b). Dry vagina during intercourse, a result of hormonal depletion, can also be classified in this category (Cull et al., 2001; Greimel et al., 2003a, 2003b).

3. Existing instruments for assessment of HRQoL
We have at present two systems of disease-specific instruments for assessment of HRQoL of patients with ovarian cancer: the Functional Assessment of Cancer Therapy (FACT) and the European Organisation for Research and Treatment of Cancer (EORTC). Both have a generic core questionnaire, the FACT-G and the EORTC QLQ-C30, and a disease-specific supplementary questionnaire, the FACT-O and the EORTC QLQ-OV28.

3.1 The FACT system: FACT-G and FACT-O
3.1.1 The scale structure of the FACT system
The FACT-G was developed as a general measure for HRQoL of patients with cancer in 1987 (Cella et al., 1993) and validated in patients with different cancers before the development of ovarian specific scale (Weitzner et al., 1995; Cella, 1995; List at al., 1996; Brady at al., 1997; Esper at al., 1997; Yellen at al., 1997; McQuellon et al., 1997; Ward at al., 1999). The instrument contains four domains and 27 questions: physical well-being (PWB), 7 questions; social / family well-being (SWB), 7 questions; emotional well-being (EWB), 6 questions; and functional well-being (FWB), 7 questions (Cella et al., 1993). Each question has 5 options: 0 (not at all), 1 (a little bit), 3 (quite a bit), and 4 (very much). All item scores are recoded to make a high score corresponding to better HRQoL. It can be seen either as a disease-specific instrument vs. other diseases or a generic instrument for all patients with cancer. An ovarian cancer-specific subscale (OCS) was developed in 1998 using the same option format (Cain et al., 1998) and was reported to have good reliability and validity in 2001 (Base-Enquist et al., 2001). The questionnaire contains one domain, originally 12 questions: stomach swelling, losing weight, vomiting, hair loss, stomach cramping, and concerns about fertility (negative questions); bowel control, good appetite, appearance, getting around, feel like a woman, and interested in sex (positive questions, reverse coded). One question (concerns about fertility) was deleted because most patients are beyond childbearing age. The two instruments are used together when assessing HRQoL of patients with ovarian cancer. The score of each scale is a summation of recoded question scores within each scale. The total score is a summation of all scores of all 38 (27 and 11) questions together.

3.1.2 Reliability and validity of the FACT system in patients with ovarian cancer
Reliability and validity of the FACT-O with FACT-G were reported by Base-Enquist et al. (2001). The internal consistency (Cronbach’s alpha) coefficient of the 11 questions in FACT-O was 0.92, and test-retest correlation coefficient of the total FACT-O score was 0.81. The correlation coefficients between the total FACT-O score, subscale scores of FACT-G, and...
subscale scores of other related instruments were as expected (good convergent and divergent validity). The scores of subscales of the FACT-G and the total FACT-O score were significantly different in different performance and treatment status, and were sensitive to changes of performance status. According to the validation results, the FACT-O is a reliable and valid instrument used with the FACT-G in assessment of ovarian cancer-specific HRQoL as a whole for patients with ovarian cancer.

3.2 The EORTC system: QLQ-C30 and QLQ-OV28

3.2.1 The scale structure of the EORTC system

The development of the EORTC QLQ-C30 can be traced back in 1986. The questionnaire was designed for the measurement of general HRQoL issued for patients with cancer (Aaronson et al., 1993). It can also be seen either as a disease-specific instrument vs. other diseases or a generic instrument for all patients with cancer. The questionnaire contains 30 questions belonging to five functional scales (physical, role, emotional, social, and cognitive), nine symptom scales (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, and diarrhea), financial difficulty in the past week, and one global health status (overall health and quality of life) scale. Each question has 4 options: 1 (not at all), 2 (a little), 3 (quite a bit), and 4 (very much). Each scale is scored separately. There is no total score. All scale scores are transformed into 0-100 from a recoded summation of item scores in each scale. For all functional scales, a higher score represents a better HRQoL. For all symptom scales and financial difficulty, a higher score means a poorer HRQoL. Previous studies showed good reliability and validity for different cancer diagnoses (Bjordal & Kaasa, 1992; Aaronson et al., 1993; Hjermstad et al., 1995; Groenvold et al., 1997; Kobayashi et al., 1998).

The EORTC QLQ-OV28 was designed as a supplement to the EORTC QLQ-C30 for the use in ovarian cancer clinical trials and related studies (Cull et al., 2001; Greimel et al., 2003a, 2003b). It contains seven subscales and 28 questions – abdominal / gastrointestinal symptoms (7 questions: abdominal pain, feeling bloated, clothes too tight, changed bowel habit, flatulence, fullness when eating, indigestion), peripheral neuropathy (4 questions: tingling, numbness, and weakness), other chemotherapy side-effects (7 questions: hair loss and upset by hair loss, taste change, muscle pain, hearing problem, urinary frequency, and skin problem), hormonal / menopausal (2 questions: hot flushes and night sweat), body image (2 questions: less attractive, dissatisfied with body), attitude to disease and treatment (3 questions: disease burden, treatment burden, and worry about future), and sexual function (4 questions: interest in sex, sexual activity, enjoyment of sex, and dry vagina). Each scale is scored separately as that of the EORTC QLQ-C30. For symptom scales, a higher score means a poorer HRQoL. For function scales (body image and sexual function), a higher score represent a better HRQoL. In addition to the cross-cultural validation of the EORTC, Chie et al. (2010) reported the translation and validation of the EORTC QLQ-OV28 in Taiwan and found a relatively low importance of body image, menopausal, and sexuality problems because of low emphasis on attractiveness and avoidance of sexual activity after having cancer.

3.2.2 Reliability and validity of the EORTC system in patients with ovarian cancer

Greimel et al. (2003b) reported the result of cross-cultural validation of the EORTC QLQ-OV28 used with the EORTC QLQ-C30. The internal consistency (Cronbach’s alpha) coefficients of all subscales except body image (0.58) were above 0.70 (ranging from 0.77 to
0.90). There was no scaling error except the subscale of other chemotherapy side effects (5/42). The intraclass correlation coefficients for test-retest of all subscales ranged from 0.74 to 0.94. The correlation coefficients between subscales of the EORTC QLQ-OV28 and EORTC QLQ-C30 were as expected. For responsiveness, scores of abdominal symptoms, peripheral neuropathy, other chemotherapy side effects, and disease burden responded significantly after treatment. For sensitivity (known-groups comparison), subscale scores differed most significantly between patients with primary and recurrent tumors. According to the validation report, the EORTC QLQ-OV28 is a reliable and valid multi-dimensional instrument used with the EORTC QLQ-C30 for the assessment of HRQoL of multiple aspects for patients with ovarian cancer.

3.3 Comparison of scale structures of the two systems
The comparison of the two sets of instruments is shown in Tables 1 and 2. The functional scales of the FACT-G and the EORTC QLQ-C30 are similar. Both include physical, mental or emotional, social, and role or functional subscales. The FACT-G emphasizes familial functioning, while the EORTC QLQ-C30 includes cognitive functioning. Both have an overall measure for HRQoL: the FACT-G uses a summation of all scores, while the EORTC QLQ-C30 measures it separately. The EORTC QLQ-C30 also has symptom and financial difficulty subscales. The FACT-G includes some symptoms in physical or function subscales (Table 1). The contents of the FACT-O and the EORTC QLQ-OV28 are similar. However, the FACT-O has only one overall scale for ovarian cancer, while the EORTC QLQ-OV28 has seven subscales covering problems of different organ-systems or aspects of HRQoL (Table 2).

<table>
<thead>
<tr>
<th>FACT</th>
<th>EORTC</th>
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<tbody>
<tr>
<td>Physical</td>
<td>Physical</td>
</tr>
<tr>
<td>Energy</td>
<td>Strenuous activity</td>
</tr>
<tr>
<td>Nausea</td>
<td>Long walk</td>
</tr>
<tr>
<td>Family needs</td>
<td>Short walk</td>
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<tr>
<td>Pain</td>
<td>Stay in chair</td>
</tr>
<tr>
<td>Side effects</td>
<td>Self-care</td>
</tr>
<tr>
<td>Feel ill</td>
<td></td>
</tr>
<tr>
<td>Bed-ridden</td>
<td></td>
</tr>
<tr>
<td>Social/family</td>
<td>Social</td>
</tr>
<tr>
<td>Close to friends</td>
<td>Interfere with family life</td>
</tr>
<tr>
<td>Family support</td>
<td>With social activities</td>
</tr>
<tr>
<td>Friends’ support</td>
<td></td>
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<tr>
<td>Family comm. illness</td>
<td></td>
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<tr>
<td>Close to partner</td>
<td></td>
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<tr>
<td>Sexual life</td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>Emotional</td>
</tr>
<tr>
<td>Feel sad</td>
<td>Tense</td>
</tr>
<tr>
<td>Satisfied with coping</td>
<td>Worry</td>
</tr>
<tr>
<td>Losing hope</td>
<td>Irritable</td>
</tr>
<tr>
<td>Feel nervous</td>
<td>Depressed</td>
</tr>
<tr>
<td>Worry / dying</td>
<td>Concentration</td>
</tr>
<tr>
<td>Worry / getting worse</td>
<td>Remembering</td>
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</table>
### FACT EORTC

<table>
<thead>
<tr>
<th>Functional</th>
<th>Role</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Able to work</td>
<td>Limited work</td>
<td>Pain, Fatigue, Nausea &amp; vomiting</td>
</tr>
<tr>
<td>Work fulfilling</td>
<td>Limited leisure</td>
<td>Dyspnea, Sleep, Appetite, constipation, diarrhea</td>
</tr>
<tr>
<td>Enjoy life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep well</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enjoy pleasure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Content with QOL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall Health</td>
<td>QOL</td>
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**Table 1. Comparison of FACT-G and the EORTC QLQ-C30.**

<table>
<thead>
<tr>
<th>FACT</th>
<th>EORTC</th>
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<tbody>
<tr>
<td>FACT-O (one scale)</td>
<td>GI symptoms</td>
<td>Abdominal pain, Feeling bloated, Clothes tight, Changed bowel habit, Flatulence, Fullness when eating, Indigestion</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>Tingling, Numbness, Weakness</td>
</tr>
<tr>
<td></td>
<td>Other chemotherapy side effects</td>
<td>Hair loss &amp; upset, Taste change, Muscle pain, Hearing problem, Urinary frequency, Skin problem</td>
</tr>
<tr>
<td></td>
<td>Attitude to disease</td>
<td>Disease burden, Treatment burden, Worry about future</td>
</tr>
<tr>
<td></td>
<td>Sexual function</td>
<td>Interest in sex, Sexual activity, Sex enjoyment, Dry vagina</td>
</tr>
</tbody>
</table>

**Table 2. Comparison of FACT-O and the EORTC QLQ-OV28.**
4. Equivalence of the FACT and the EORTC systems

Are the results of the two systems equivalent? Hozner et al. (2006) reported a study on 737 patients with different cancers for the equivalence of the FACT-G and the EORTC QLQ-C30, the core content of the two systems. Both classical test theory and Rasch measurement model were used. Three of the four subscales common to the two systems are equating: physical, emotional, and role / functional, but not the social / family subscale. A converting table was generated according to the results. No such study was conducted for the FACT-O and the EORTC QLQ-OV28 because the FACT-O has only one subscale, therefore the two site-specific questionnaires have no common subscales to study.

5. Application of two systems in assessing HRQoL of patients with ovarian cancer undergoing different treatments across different cultures

5.1 The application of the FACT system

The two systems of instruments measuring HRQoL of patients with ovarian cancer were used in clinical trials and non-trial clinical studies. The FACT system was more widely used because the FACT-O was developed earlier than the EORTC QLQ-OV28. The FACT-O has been applied in studies assessing palliative chemotherapy for advanced ovarian cancer (using EORTC QLQ-C30 and FACT-O) (Doyle et al., 2001), general chemotherapy (Le et al., 2004), adjuvant and salvage chemotherapy for advanced ovarian cancer (Le et al., 2005), interval cytoreduction in advanced ovarian cancer (Wenzel et al., 2005), active coping (Canada et al., 2006), Thallidomide therapy (Gordinier et al., 2007), phase I/II gemcitabine and doxorubicine (Goff et al., 2003) and phase II gemcitabine and topotecan trials for platinum-refractory ovarian cancers (Goff et al., 2008), and factors for decreased QoL (von Gruenigen et al., 2009). In summary, the FACT-O and FACT-G scores became better when there was response to treatment, active coping can improve HRQoL, and factors causing decreased HRQoL can be detected and managed in advance.

5.2 The application of the EORTC system

The use of the EORTC QLQ-OV28 with the EORTC QLQ-C30 was less common because it was developed later than the FACT-O. The two questionnaires were first used in a study assessing HRQoL for patients after pelvic exenteration in 2004 (Roos et al., 2004) where more physical, social, and sexual problems, especially for young patients were reported after surgery. A comparison of HRQoL of patients with early vs. advanced ovarian cancer (Mirabeau-Beale et al., 2009) found comparable HRQoL in two groups. A clinical trial of neoadjuvant platinum-based chemotherapy followed by (interval) debulking surgery vs. standard care of primary debulking surgery followed by platinum-based chemotherapy in stage IIIC or IV ovarian cancer used the two questionnaires did not detect any difference between the two arms in HRQoL (Vergote et al., 2010). The EORTC QLQ-C30 alone without the EORTC QLQ-OV28 has been used in a randomized trial of cisplatin / paclitaxel vs. carboplatin / paclitaxel and found patients undergoing carboplatin / paclitaxel treatment had better HRQoL (Greimel et al., 2006). Another study using the EORTC QLQ-C30 assessing the HRQoL of long-term survivors of ovarian cancer found long-term survivors had better HRQoL scores before treatment than short-term survivors, and long-term survivors had significant improvement of HRQoL in emotional and global health scores 1 year after treatment and remained stable. The scores of all domains but dyspnea were comparable with women without cancer (Greimel et al., 2011).
5.3 A comparison of the two systems in HRQoL assessment

A review article in 2010 commented after comparing all generic and specific questionnaires for HRQoL of patients with gynecologic cancers that there is little evidence that disease-, symptom- or treatment-specific instruments are more responsive or sensitive than generic or cancer-specific questionnaires, and a superior quality and quantity data reported for the FACT system compared with the EORTC system (Luckett et al., 2010). Nordin and Greimel on behalf of the EORTC Quality of Life Gynecology Group (2010) responded in a letter that such comments are not substantiated and provided examples of good results of cross-cultural validation. In addition to the cross-cultural nature, the multi-dimensional structure of the EORTC system may also help clinical researchers and practitioners conduct more detailed assessment of different aspects of HRQoL of patients.

6. Future development

Ovarian cancer is an important gynecological cancer which affects the survival and HRQoL of patients (International Agency for Research on Cancer, 2011). The keys to improve both survival and HRQoL are methods of early detection (US Task Force of Preventive Services, 2011) and effective treatment (du Bois at al., 2005; Brisow & Chi, 2006). We expect breakthroughs in both early detection and effective treatment in the near future. Patient-reported outcomes have been recommended as endpoints of clinical trials by the U.S. Food and Drug Administration (FDA) (2011). To evaluate the effectiveness of these methods, HRQoL is an essential primary endpoint. Two systems of HRQoL assessment, i.e. the FACT and the EORTC systems are available. Both cover major issues of HRQoL and show good reliability and validity in previous reports and are used widely around the world in clinical trials and clinical studies. Therefore, we expect that the assessment of HRQoL of patients can be routinely included in clinical researches and practice, to understand and further improve patients’ HRQoL.

7. Conclusions

Ovarian cancer is one of the leading female cancers around the world. There is no effective method of early detection. When detected, the stages are usually advanced, and patients have poor health-related quality of life (HRQoL). The standard treatments of this disease including debulking surgery and chemotherapy can improve survival and may have either positive or negative impacts on HRQoL of patients. The disease recurs easily. Patients may suffer repeating debulking surgeries and chemotherapies that affect their HRQoL. In this chapter, we introduced and reviewed the scale structures, psychometric properties and clinical validities of existing instruments – the FACT system and the EORTC system for the assessment of HRQoL for patients with ovarian cancer, and report the results of their application in clinical trials and observational studies. We hope that HRQoL can be emphasized and routinely assessed for all patients with ovarian cancer in future clinical researches and practice.

8. References


Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details the molecular biological aspects of ovarian cancer. It provides molecular biology techniques of understanding this cancer. The techniques are designed to determine tumor genetics, expression, and protein function, and to elucidate the genetic mechanisms by which gene and immunotherapies may be perfected. It provides an analysis of current research into aspects of malignant transformation, growth control, and metastasis. A comprehensive spectrum of topics is covered providing up to date information on scientific discoveries and management considerations.

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