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Health-related quality of life in ovarian cancer patients and its impact on clinical management

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Abstract

Although the incidence of ovarian cancer is less than that of other female cancers, the morbidity and mortality associated with the disease course is high. Because treatment involves radical surgery and intense courses of chemotherapy, health-related quality of life (HRQOL) is often compromised. Most patients recur post-first-line therapy and undergo multiple rounds of chemotherapy. Thus, HRQOL is further disrupted. As the ongoing search for optima therapies in both the first-line and recurrent setting continues, much attention is paid towards clinical trial design and implementation. Over the last decade, patient-reported outcomes and HRQOL measurement have become an integral part of these trials. HRQOL data are valued in examining the extent of treatment benefit and therefore can aid in decision-making during active treatment and palliative care. HRQOL and patient-reported outcome measurement is also useful in determining symptom prevalence, severity and management. This article highlights the state of the science of HRQOL measurement in clinical trial design and outcomes. In addition, symptom management in ovarian cancer and its ability to modulate quality of life will be explored.

Keywords

clinical trials; ovarian cancer; quality of life; symptom management

Of the 21,880 ovarian cancers estimated for the USA in 2010, there were 13,850 deaths from ovarian cancer in the same year [1]. Ovarian cancer accounts for most of the deaths from gynecologic cancers. With only 15% diagnosed at an early stage, in general the 5-year survival rate is only 46% [1]. Most women diagnosed in an advanced stage will recur and with each recurrence the chance of cure diminishes. As diagnosis at an early stage is unlikely, women often present in advanced stages with compromised physical and emotional

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wellbeing [2]. The domains of physical, emotional, functional and social wellbeing all contribute to health-related quality of life (HRQOL).

From diagnosis to death, HRQOL must influence clinical management. Changes in HRQOL, based on disease trajectory, will be discussed in this article. Unfortunately screening and early detection of ovarian cancer is suboptimal, with limited useful technologies to aid in early-stage diagnosis. In the first-line approach to treatment of ovarian cancer, the goal is to aggressively eradicate disease with surgery and chemotherapy without severely compromising HRQOL. In the treatment of recurrence, the approach becomes one which adequately stabilizes, or even reverses, disease growth, with a perhaps greater emphasis on maintaining quality of life (QOL) in the setting of perhaps, at best, a partial response to therapy.

Throughout diagnosis, frontline treatment and recurrence, QOL can and has been measured by patient-reported outcomes (PROs) to support therapeutic decision-making. The importance and simultaneous challenge of QOL data is to ensure any benefits of therapy are weighed against adverse effects. This becomes increasingly important as women with recurrent disease may experience cycle after cycle of chemotherapy with cumulative adverse effects when potential benefits become less apparent. It is from these measurements that we begin to better understand the prevalence of symptoms and hypothesize better management strategies. Symptom management thus spans from diagnosis to end-of-life care. However, there may be some difficulty in recognizing whether a statistically significant difference is clinically important secondary to the fact that the data are dependent on the variability of the measurement tools.

Screening/early diagnosis

Unfortunately, approximately 60% or more of ovarian cancers are diagnosed in advanced stages [1]. Effective screening programs and/or individual tests have yet to be clearly defined. Although ovarian cancer is most often fatal, it is relatively uncommon as compared with other cancers in women, such as breast or lung, which perhaps makes ovarian cancer screening trials expensive and less effective. Although QOL measurement in clinical trials evaluating therapeutic options for ovarian cancer is common, its use in the screening literature is limited. More commonly discussed is the impact of false-positive screening on QOL in cervical or breast cancer. Most QOL data in ovarian cancer screening lies in populations at high risk, such as those with genetic mutations undergoing risk-reducing salpingo-oophorectomy (RRSO). In addition, in the RRSO population, screening is more a process of early detection or diagnosis rather than a true screening test.

In general, the data are mixed regarding the negative impact of these screening tests on QOL [3]. The US National Cancer Institute’s Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial was a large trial to determine whether annual screening tests could reduce disease-related mortality [3]. For the ovarian cancer screening group, women underwent annual CA-125 blood tests and pelvic ultrasounds. QOL was also measured using the Short Form (SF)-12 Physical and Mental Component Scales at each assessment. A cancer-specific distress scale was also used to measure satisfaction with the decision to participate in the

trial, as distress may indicate dissatisfaction and discomfort with the intervention of the trial. In this study, although not described as specific to ovarian cancer screening, participants with false-positive tests had higher levels of intrusive thoughts about cancer, yet this effect did not appear to be long-lasting. Women and participants with a first-degree relative with cancer were also more likely to have these intrusive thoughts. The participants with false-negative tests were also less likely to comply with further testing. The authors conclude that in screening trials it may be important to intervene on the part of the participants with false negative results as to decrease the potential stress involved in screening trials. Of note, those assigned to the control group did not have statistically significant differences in HRQOL, contrary to the belief that the mere ability to be involved in a cancer screening process alleviates stress associated with an unknown risk for cancer.

There are several studies examining HRQOL in RRSO. In a cross-sectional study of 846 high-risk women, 44% had undergone RRSO as compared with others who opted for periodic gynecologic exams [4]. Although ‘generic’ QOL as measured by the SF-36 did not appear to differ between the groups, in general the RRSO group did report fewer concerns regarding their risk for cancer. Unfortunately, these women also had significantly more menopausal symptoms and worse sexual functioning relating to pleasure and discomfort than the women who underwent gynecologic examination alone. In 2009, Fang *et al.* described prospectively collected data on QOL, sexual functioning, body image and depressive symptoms in 75 women undergoing RRSO versus serial screening [5]. The women who underwent surgery reported poorer physical functioning, role limitations, pain, and social and sexual functioning at the 1-month assessment. Most deficits resolved by 6 months, however, the RRSO group had persistent menopausal complaints. Kauff *et al.* also published on the impact of ovarian cancer screening on QOL. In this study of 135 patients, abnormal ovarian cancer screening results were associated with a significant decrease in the Mental Component Summary form of the SF-36 [6]. Finally, the Gynecologic Oncology Group (GOG) also published initial data regarding RRSO and CA-125 in women at risk for ovarian cancer (GOG 199) [7]. The study included QOL measurement, however, data have yet to be published. Future work should perhaps target the RRSO group in terms of preoperative counseling, postoperative recovery and treatment of menopausal symptoms.

First-line therapy

The initial approach to the treatment of ovarian cancer involves debulking surgery and adjuvant chemotherapy. The standard approach is to attempt an optimal cytoreductive surgery followed by either intravenous or intraperitoneal chemotherapy. The measurement of HRQOL has been incorporated in many clinical trials of the first-line treatment of ovarian cancer (Table 1). HRQOL has been used to argue in favor (or against) novel therapies and has proven to be a prognostic indicator for treatment outcomes.

The GOG published two trials that specifically incorporated the measurement of QOL in the design of the trial. In 2005, Wenzel *et al.* reported on the HRQOL changes with interval secondary cytoreduction for those patients who were initially sub-optimally cytoreduced [8]. At the four time-point assessments, the majority (approximately 80% or more) of patients completed all measures. Overall, there were no appreciable differences in QOL between the

groups. In this study, the midtreatment baseline QOL score, as measured by the functional assessment of cancer therapy – ovarian (FACT-O), indicated that higher QOL scores were associated with improved overall survival (OS) among all patients. This has also been demonstrated in other trials. Carey *et al.* described the Canadian experience of QOL and performance status as they relate to progression-free survival (PFS) and OS in a frontline chemotherapy trial for ovarian cancer [9]. Both global QOL and performance status were associated with PFS and OS, thereby confirming the findings of Wenzel *et al.* in the USA in 2005.

In 2007, Wenzel *et al.* published the QOL data from GOG protocol 172 which examined the use of intraperitoneal chemotherapy, versus intravenous, for advanced ovarian cancer [10]. QOL measurement was particularly important in this trial as it was the first Phase III GOG ovarian cancer trial that proposed a change in route for the administration of front-line chemotherapy. OS was improved by approximately 16 months in the intraperitoneal arm, however, HRQOL was significantly worse during active treatment and many patients did not complete all prescribed regimens secondary to toxicity. Specifically, during active treatment patients on the intraperitoneal arm experienced more HRQOL disruption, abdominal discomfort and neurotoxicity compared with those receiving conventional intravenous therapy. However, only neurotoxicity remained significantly greater for intraperitoneal patients 12 months post-treatment. Notably, studies are currently being conducted to mitigate the added burden associated with intraperitoneal therapy while hopefully maintaining survival benefit.

Since 2006, several sentinel non-GOG trials must also be highlighted in the first-line treatment of ovarian cancer. First, in 2010, Vergote *et al.* reported the results of a Gynecologic Cancer Intergroup Collaboration trial which compared upfront debulking followed by chemotherapy to neoadjuvant chemotherapy [11]. As the standard approach to treatment has historically been surgical cytoreduction followed by chemotherapy, this was the first randomized Phase III trial of this alternative strategy. In this trial, patients completed QOL assessments using European Organization for Research and Treatment of Cancer (EORTC)-validated instruments. The authors reported similar survival outcomes in the two groups with both perioperative and postoperative morbidity being higher in the upfront surgery group. Of note however, the Quality of Life Questionnaire-C30 global health scores were not significantly different between the two groups. The HRQOL measurement in this study did not seem to correlate with the ‘toxicity’ (morbidity/mortality) demonstrated with upfront, as compared with interval, surgery. Future publications will hopefully elaborate on the QOL data to help to explain this finding.

A second trial from Germany reported the QOL data from a Phase III trial evaluating carboplatin versus cisplatin and paclitaxel [12]. Although PFS and OS did not differ between the groups, QOL data indicated significant improvements in the TC arms across multiple scales. These data helped justify the change in therapeutic decision-making by using a patient-reported tool alone. The toxicity data presented in the manuscript is matched with the QOL data in a table to describe how the PRO mirrors the toxicity information to some degree. In general, it is of note that there appears to be a lack of correlation between hematologic and pain toxicity with the QOL functioning scales. Certainly there has been

speculation that toxicity scales under-report patient's complaints [13]. This perhaps requires future examination and may relate more specifically to the European QOL instruments.

Recurrent disease

In the approach to treating recurrent ovarian cancer, tumor control without compromising HRQOL should be the goal of therapy [12]. There has yet to be a Phase III trial reported by the GOG that involves QOL assessments for recurrent ovarian cancer. However, there are multiple international trials (Table 2). Recently, the Gynecologic Cancer Intergroup reported the use of HRQOL measurement in their large trial of Carboplatin and Paclitaxel versus Carboplatin and Pegylated Liposomal Doxorubicin for Recurrent Platinum Sensitive Ovarian Cancer [14]. QOL was measured every 3 months for 1 year from the date of enrollment. Although the QOL data have not been formally presented as of yet, the doxorubicin arm was significantly less toxic and it will be of interest to see if the toxicity data are relevant to the QOL measurements. In a German trial of nonplatinum doublets with topotecan versus topotecan alone, QOL measurements were also used [15]. However, in this study, the doublet therapy provided no survival advantage, nor did it demonstrate differences in QOL scores. Of note, in general combined therapy was associated with higher incidence of hematologic toxicity, yet this did not seem to be reflected in the QOL data. However, a detailed description of the data is lacking. In general it appears that HRQOL data in the recurrent setting is deficient in terms of detailed descriptions of QOL disruptions and numbers of studies including QOL measurements.

Some may argue that QOL measurement in this setting is of particular importance, being that therapy will often fail. This argument relates well to another sentinel paper published by Rustin *et al.* in 2010 [16]. This study examined the impact of early versus delayed treatment of recurrent ovarian cancer based on CA-125 measurements exceeding twice the upper limit of normal. In patients where the CA-125 result was masked, treatment was initiated at clinical or symptomatic recurrence. The findings suggested that early treatment did not improve survival and unfortunately time to deterioration in QOL scores was shorter by several months in the early treatment group. This was seen across almost all QOL subscales. The QOL data here is noteworthy. In future studies, it may be of interest to perform cost–effectiveness analysis where quality-adjusted life years are considered because if therapy is costly, and QOL suffers, argument can be made to adjust therapeutic interventions.

Symptom management

In the discussion of HRQOL in palliative care and survivorship for women with ovarian cancer, the approach to therapy and QOL may be symptom driven [17]. Patient-reported outcomes during clinical trials involving cancer therapeutics helps to pave the way toward improved acceptance of new treatment regimens. Patient-reported data reaches beyond toxicity or Common Toxicity Criteria in multiple instances (Table 3). Beyond the support of new cancer therapeutics, is the acknowledgement and management of the various symptoms that are contributing to QOL changes. The approach to symptom control in patients undergoing cancer therapy requires the use of an appropriate measurement tool as well as a multidimensional treatment plan consisting of both behavioral and pharmaceutical

interventions. The FACT physical wellbeing subscale has been described by some to be associated with outcomes in a significant manner [18]. The physical wellbeing subscale examines some of the most common symptoms that will be discussed here: fatigue, bloating and pain. In addition, peripheral neuropathy and sexual dysfunction will be addressed as they have obvious implications in gynecologic cancers. For each item discussed in the following section, recent noteworthy studies in measurement, behavioral and therapeutic interventions will be highlighted.

Fatigue

Cancer-related fatigue (CRF) is fatigue that is not relieved by rest or sleep [19]. Fatigue affects the majority of patients undergoing cancer treatment – approaching 96% of women with cancer [20]. Fatigue may be the top-ranked symptom among multiple cancer types [21]. Specifically, CRF has been described in the ovarian cancer population and is a symptom that appears to affect women across all stages and influences other factors involved in general QOL, such as social or functional wellbeing. Holzner *et al.* examined the prevalence of fatigue in ovarian cancer survivors, with hemoglobin levels over 10 g/dl. A total of 32.7% of patients in this study of 98 women reported suffering from fatigue [22]. In a study comparing early- to advanced-stage ovarian cancer patients, fatigue scores on the FACT-Fatigue were equal in terms of mean reported scores [23]. Fatigue, as reported by the EORTC-Fatigue scale, correlated with lower QOL, less spirituality, increased fear of recurrence and lower emotional status in both early and advanced cases. There are many single and multiple item patient-reported measures to document fatigue. Specifically, in a systematic review of measures used to assess fatigue, Minton and Stone describe how the multiple item FACT-Fatigue and the EORTC quality of life questionnaire-C30 fatigue subscale are widely administered and well-validated tools, as opposed to the single-item scales, used to assess fatigue [24]. However, there is some evidence that the symptom-specific instrument, such as the FACT-Fatigue, offers little advantage over the more general measures such as the FACT-O [25]. More evidence is needed to establish whether fatigue-specific instruments offer an advantage over more general measures that include fatigue as one of several symptoms assessed.

In the measurement of fatigue, perhaps treatable causes of fatigue, such as anemia or depression, need to be ruled out to aid with more directed interventions. Yet, it may become difficult to determine if the fatigue itself led to more anxiety and depression as the two diagnoses have been well correlated [22]. In a study by Matulonis *et al.*, 58 early-stage ovarian cancer survivors were surveyed and better mental health was associated with less fatigue, as reported by the FACT-F [26]. Traeger *et al.* describe an analysis of cancer patients in general and the correlation of clinical depression in the presence of CRF [27]. This describes a novel approach of using a pattern seen on a measure to predict a secondary diagnosis, such as depression, which may aid in identifying symptoms contributing to fatigue. More recently, investigators have looked into physiologic explanations for CRF. Weinrib *et al.* have presented interesting data regarding the alterations in Cortisol levels and its association with fatigue [28]. After a study of 100 patients with ovarian cancer, they proposed that higher nocturnal Cortisol and lower Cortisol variability were significantly associated with fatigue. A small pilot study in breast cancer patients examined whether yoga

could regulate Cortisol secretion levels and alter fatigue levels. With this intervention, women had lower salivary Cortisol levels and improved fatigue scores [29].

Management of fatigue requires a multidisciplinary approach to diagnosis and treatment. For example, acupuncture is perhaps an underutilized complementary therapy in ovarian cancer patients. Dean-Clower *et al.* describe the use of acupuncture in 32 patients treated at their institution. After an 8-week outpatient acupuncture therapy, improvements in fatigue were documented immediately post-therapy, with a sustained benefit up to 12 weeks [30]. In another study by Stevinson *et al.*, ovarian cancer survivors who reported lower fatigue were those who met public health physical activity guidelines [31]. Similarly, an intervention of restorative yoga which is a 'gentle' type of yoga that encourages relaxation, helped to reduce fatigue in 37 ovarian cancer patients [32]. Thus, simple exercise/physical activity interventions may provide relief for women reporting fatigue after remission. In the Workflow Information Systems for European Nursing Care intervention, symptoms were reported by patients in a cyclical manner and then specifically target based on severity by nurses. Only 13 ovarian cancer patients were included in this study. Unfortunately, the intervention did not seem to affect patient-reported fatigue reported by the Chemotherapy Symptom Assessment Scale measure. Although approximately 50% of patients reported fatigue and 50% of those reported it to be moderate-to-severe, the authors speculate that it is the complexity of the symptoms that makes both accurate measures and successful interventions difficult to develop [20]. Other interventions, specifically pharmaceutical-based therapies, have been described in the literature but they are not particular to ovarian cancer and will thus not be covered here, however, this is an area for future investigation [33]. Other areas of future research may involve novel means to assess and manage symptoms such as fatigue by using email or text messaging to communicate more efficiently with patients [34,35].

Bloating

The first item of the ovarian cancer subscale in the FACT-O states 'I have swelling in my stomach area'. Abdominal distension may wax and wane during the trajectory of ovarian cancer. Many patients with advanced disease present with malignant ascites and thus distension at the time of diagnosis. This usually dissipates quickly after surgery or during intravenous chemotherapy however may persist in the setting of intraperitoneal chemotherapy [36]. Abdominal distension may then again present itself in the recurrent and/or end-of-life phase where its management may be critical to the success of palliative care. Some have reported that the mere presence of massive ascites is a significant variable in terms of predicting short- versus long-term survival [17].

In 2006, the GOG published results of their Phase III trial using intraperitoneal chemotherapy as a primary adjuvant treatment for advanced ovarian cancer [8,36]. The group used a four-item specific abdominal discomfort scale to quantify patient's abdominal symptoms with this type of treatment. This patient-reported measure proved to be more reliable than the toxicity-criteria measurements. In the GOG study, the abdominal discomfort scale correlated with the physical wellbeing scale and the Trial Outcome Index, which is a combination of the physical, functional and ovarian cancer specific subscales. Of

note, the emotional and social wellbeing scales were less well-correlated with the abdominal discomfort scale. Perhaps this can be partially explained by a report by Husain *et al.* regarding ascites symptom cluster in patients referred for paracentesis [37]. In this study, at both pre- and post-paracentesis, there were two clusters of symptoms (symptoms that commonly occur together): 'depression–anxiety' and 'fatigue–appetite–well-being–mobility'. In this study, paracentesis tended to improve single symptoms such as distension and dyspnea; however, of note, is the decline in the cognitive domain of QOL. Similar to the GOG study already described, the physical complaint of abdominal distension alone may not clearly correlate with emotional or cognitive changes. This area needs further investigation, but does support the use of unique scales to measure abdominal discomfort alone as opposed to clustered in larger QOL scales.

In the treatment of symptomatic ascites, paracentesis has been shown to provide immediate symptom palliation [38]. This therapy proved beneficial in multiple physical complaints such as dyspnea and appetite loss, however, of interest is the marked deterioration in cognitive and emotional scales such as anxiety and fatigue. This is perhaps because paracentesis provides only temporary relief and often requires repetitive procedures over short periods of time. A recent Cochrane review attempted to search for trials examining the management of multiple paracentesis in women with malignant ascites and a diagnosis of gynecologic cancer [39]. Unfortunately, no trials were identified and thus recommendations could not be generated regarding the efficacy, safety and QOL effects of this therapy. Thus this review emphasizes the need for future studies to address abdominal discomfort and the approach to and effect of paracentesis.

Future trials may also approach the management of malignant ascites with pharmaceutical interventions such as intraperitoneal or intravenous antibodies specific to targeting malignant ascites. For example, in 2008, Hamilton *et al.* reported the use of intraperitoneal bevacizumab in a case report for the management of severe symptomatic ascites [40]. This report is optimistic in terms of palliative and short-term relief of symptoms in the end-of-life period.

Pain

In ovarian cancer patients with the lowest QOL scores, pain has been described to contribute significantly to this QOL deficit [41]. However, in an examination of QOL-related toxicities, grade 3–4 myalgias appeared to be more tolerable symptoms than perhaps febrile neutropenia, fatigue or nausea/vomiting [42]. Although pain alone may not be particularly distressing or life-changing for some patients, pain has been shown to be linked to fatigue, which is consistently reported to be an extremely concerning and distressing symptom for cancer patients [21]. In general, pain may also be associated with poor mental health and may be reported differently depending on the mental status of the patient. For example, when examining early stage ovarian cancer survivors, there was a subset of patients (~40% of 58 patients) who scored below the norm on the Mental Health Inventory-17 survey. Those women who had better mental health were found to have less physical complaints such as pain [26].

In general, pain during the postoperative and adjuvant chemotherapy period tends to improve (as compared with pretreatment or pre-operatively) [43]. However, when 200 women without evidence of active disease for 2 years were surveyed, 53.5% reported current pain or discomfort [44]. In the group of women with pain, 21% reported the pain as severe and 21% reported that the pain affected their lives. Pain is likely to become even more relevant to QOL dysfunction in the recurrent or end-of-life period [45›46]. The National Comprehensive Cancer Network provides algorithms for pain management in cancer patients in general. Future studies in ovarian cancer patients may require closer attention to the management of pain in the recurrent or end-of-life period and specific recommendations for pain management in women with perhaps unique abdominal symptoms.

Peripheral neuropathy

Peripheral neuropathy in the ovarian cancer patient is most often treatment-related. In an evaluation of the Surveillance, Epidemiology and End Results database in 2010, the incidence in ovarian cancer patients was 21.5/1000 person-years, higher than either breast or lung cancer patients [47]. Women receiving platinum-taxane chemotherapy were three-times more likely to develop peripheral neuropathy than those patients not receiving chemotherapy. While peripheral neuropathy may not be considered by patients to be as concerning as other symptoms, such as pain or fatigue, it is more likely to be long-lasting and persist after therapy [10›42].

Women with ovarian cancers who are treated with cisplatin or taxane-based regimens are at risk for developing peripheral neuropathy. Grade 2–3 sensory neuropathy and less commonly motor neuropathy, occurs in 25% of patients receiving these drugs [48]. The most common complaints are reported to be burning dysesthesias, numbness and tingling and shooting sensations in the distal extremities [49]. It has also been suggested that up to 23% of patients may suffer from residual peripheral neuropathy 48 months after treatment, which is a potential obstacle to using this regimen in the recurrent setting [49]. In 2003, Calhoun *et al*. used the FACT-general in addition to a neurotoxicity subscale (GOG-Ntx) to study patients receiving systemic chemotherapy for ovarian cancer [50]. The Ntx subscale has 11 items aimed at symptoms specifically related to the chemotherapy side effect, neurotoxicity. This measure was reliable and valid in its documentation of the effect of neuropathy on QOL as the measurement of neurotoxicity correlated with all realms of the FACT-G except social or functional wellbeing. Interestingly, neurotoxicity often worsened despite improvements in the FACT scores. It was emphasized that neurotoxicity must be measured as it might not be reliably recorded by the FACT-G alone. Specifically, in GOG 172, despite the reported benefits of interperitoneal therapy for PFS and OS, the trial demonstrated that both neurotoxicity and abdominal discomfort were more prevalent in the interperitoneal arm. Although the QOL scores improved over time, specifically at 12 months from completion of initial treatment, neurotoxicity symptoms persisted. This report has perhaps contributed to physicians being less willing to dose interperitoneal chemotherapy according to the Armstrong *et al*. regimen [10]. Thus, this patient-reported symptom and outcome is one of the first of its kind to alter physican-prescribed treatment planning.

Thus far, proposed treatments/cures for peripheral neuropathy have been disappointing. Neuropathic pain resulting from peripheral neuropathy does not respond as well to opioids and may require other management strategies that employ antidepressants or anticonvulsants [51]. Preventative therapies have also been investigated but with questionable success rates. Amifostine, a drug that could be given in tandem to chemotherapy, has been suggested to be neuroprotective; however, in clinical trials, its affect is variable and ultimately shown to have a modest to no preventative effect [52,53]. There might be an indication that oral vitamin E reduces the incidence of neurotoxicity, although most studies were small and limited owing to methodology [53,54]. Recently some data have reported a role of free radical scavengers in the treatment of neuropathic pain (of note vitamin E is also thought to be a free radical scavenger). In a study by Kim *et al.*, phenyl *N*-tert-butylnitrone, a free radical scavenger, was studied in chemotherapy-induced neuropathic pain in rats [55]. This drug prevented the development of chemotherapy-induced neuropathic pain after paclitaxel injection. Vitamin B6 (pyridoxine) has also been shown to help reduce the neurotoxicity of cisplatin and may be a useful agent in ameliorating side effects of treatment [56].

Sexual dysfunction

Sexual health has been described by four different levels of dysfunction: body image, gender role (femininity identity), sexual functioning and reproductive ability [57]. Body image and feminine identity are both affected by pelvic organ surgery, radical or not. Sexual functioning is described by Reis *et al.* to be affected by fear/anxiety, lack of desire, aches/pains, shortening of the vagina and decrease in the ability to obtain orgasm [57]. Thus sexual dysfunction is multifactorial and perhaps challenging to target.

In general, the literature is limited in terms of sexual dysfunction specific to ovarian cancer. Most of the literature is in reference to the perimenopausal or premenopausal ovarian cancer patient. In this patient population surgical menopause is related significantly to poorer sexual functioning [58]. This is perhaps a combination of abrupt hormone deficits in combination with the psychosocial impact of having ‘female’ organs removed. Premature ovarian failure induced by surgical menopause causes vaginal dryness and this physical symptom further disrupts sexual function [59]. In a study of ovarian germ cell tumor survivors, those women with fertility-preserving surgery had significantly less sexual discomfort. Regardless of fertility status, these survivors had lower scores on a sexual activity and pleasure scale although did appear to have improved shared pleasant activities with their partners [60]. In a survey of 200 ovarian cancer survivors, 57% reported a negative effect of cancer and cancer treatment on sexuality. Being married or in a stable relationship and younger age both predicted a negative effect on sexuality. Almost half of the women expressed fear of the effects of treatment on sexual relationships and physical symptoms during sexual activity [44].

Expert commentary

Health-related quality of life assessment provides supplementary information about the impact of the disease and its treatment on ovarian cancer patients. Specifically with ovarian cancer, which can be considered a chronic disease, HRQOL information can assist the

patient and caregiver in selecting antineoplastic and supportive-care therapy. Given the chronic and often incurable nature of this malignancy, the toxicity and tolerability of a specific therapy can be as important as its efficacy. Only careful evaluation of patient-reported QOL can allow evaluation of tradeoffs between symptom relief and toxicity. The advancing sophistication of HRQOL and patient-reported outcome measurement has provided a growing and much needed understanding of the specific disease and treatment-related concerns of ovarian cancer patients. It is through this measurement mechanism that targeted interventions can be rigorously evaluated. However, of note, challenges of using QOL data to inform clinical practice may include the use of somewhat arbitrary cutoff points or magnitude of change in HRQOL score to determine when therapeutic change is necessitated. Furthermore, the timing and frequency of QOL assessments may also affect this, perhaps adding to the variability in the data. This may be a drawback for medical testing in general where a range of normalcy may be better suited.

Five-year view

Through treatment advancements, it is likely that within the next 5 years both PFS and OS gains will be made. Patient-reported benefits in overall HRQOL and disease-specific symptoms will match these gains. However, additional treatment-related toxicities or symptoms may emerge and challenge current outcome measurement strategies. The NIH Patient Reported Outcomes Measurement Information System initiative will assist in meeting these measurement challenges and provide meaningful information to introduce and further evaluate clinical management strategies [101].

For example, promising advances in the treatment of ovarian cancer are forthcoming, such as the addition of biologic therapy to cytotoxic chemotherapy and/or the use of consolidation therapy after initial first-line cytotoxic therapy. These two areas have HRQOL implications and patient-reported outcomes gleaned from these therapeutic studies will help guide clinical management of ovarian cancer as a potentially chronic disease. HRQOL data obtained from the initial Phase III data from the trials using bevacizumab in the first-line treatment of ovarian cancer will be useful to more fully explain the effects of biologic therapy [61]. The use of biologic or cytotoxic therapy as consolidation after primary or recurrent treatment has yet to be well-defined and supported and strategic HRQOL assessment will provide valuable information [62].

Finally, a more detailed examination of symptom prevalence, severity and significance will emerge through analyses of patient-reported outcomes. These data will serve to promote symptom management interventions and supportive care studies, either in concert with or independent of the clinical trial setting. It is anticipated that these data sets will be linked in a manner to incorporate comparative effectiveness research questions [42]. Taken together, advances in cancer treatment and ovarian cancer patient outcome measurement will yield promising results to meet the challenges associated with ovarian cancer.

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Website

101. NIH PROMIS initiative. www.nihpromis.org

Key issues

- As diagnosis of ovarian cancer at an early stage is unlikely, women often present in advanced stages with a compromised health-related quality of life (HRQOL).
- Quality of life data can be used to influence treatment decision-making and the clinical management of ovarian cancer.
- Initial or baseline HRQOL scores can be predictive of a patient's capacity to tolerate or benefit from treatment and could be used as a stratification variable in clinical trial design and as a useful clinical tool when identifying treatment options in the palliative care setting.
- Physical, emotional, social, functional, as well as disease-specific symptoms reported by HRQOL measures have helped define the most prevalent experiences of patients during the ovarian cancer disease trajectory.
- Fatigue is perhaps the most prevalent symptom in ovarian cancer, yet the measurement and clinical management continues to be challenging.
- Cancer-related pain in ovarian cancer is often associated with and contributes to the severity of other symptoms such as fatigue, nausea/vomiting and sexual dysfunction.
- Abdominal bloating is an ovarian-cancer specific complaint and has particular impact on the management of women in the palliative or end-of-life stages in ovarian cancer.
- Sexual dysfunction in ovarian cancer patients often relates to the surgical menopause induced in younger survivors, affecting unique alterations in social and emotional wellbeing.

Table 1

Phase III clinical trials of first-line treatment of ovarian cancer with quality-of-life measurement I from 2003 to 2011. I

Trial	QOL measure	Primary trial outcome	QOL outcome	Ref.
NCT or primary surgery in Stages NIC or IV ovarian cancer	EORTC QLQ-C30 and -OV28	NCT is not inferior to primary surgery	No differences in global health scores, test for treatment effect on global health also not significant	[11]
CT with or without gemcitabine in first- line treatment	EORTC QLQ-C30 and -OV28	The addition of gemcitabine did not improve outcomes	The addition of gemcitabine showed a delaying impact on improvement of global health status; however, after the third cycle, no significant differences were seen	[62]
ip. vs iv. chemotherapy for optimally debulked ovarian cancer	FACT-TOI, -AD and -Ntx scales	ip. chemotherapy	During treatment the IP arm experienced more QOL disruption, AD and NTx; only Ntx remained significant for ip. patients 12 months after treatment	[10]
Topotecan following CT in first-line treatment	EORTC QLQ-C30 and -OV28	The addition of topotecan to CT did not improve outcomes	No statistically significant QOL differences between treatment arms despite significantly more toxicity in the experimental arm	[63]
Addition of epirubicin to CT in first-line treatment	EORTC QLQ-C30	Addition of epirubicin to CT did not improve outcomes	Control arm reported significantly better QOL with respect to worst global health score over time	[64]
PT vs CT in first-line treatment	EORTC QLQ-C30	PT and CT did not differ in terms of treatment outcomes	CT arms achieved better QOL outcomes	[12]
CD vs CT in first-line treatment	EORTC QLQ-C30 and -OV28	CD similar to CT in terms of outcomes	Global QOL health scores did not differ between groups; however, neuropathy scores were greater and more persistent in the CT arm	[65]

AD: Abdominal discomfort; CD: Carboplatin/pegylated liposomal doxorubicin: CT: Carboplatin/paclitaxel; EORTC: European Organization for Research and Treatment of Cancer; FACT-O: Functional Assessment of Cancer Therapy – Ovarian; FACT-TOI: Functional Assessment of Cancer Therapy – Trial Outcome Index; ip.: Intraperitoneal; iv.: Intravenous; NCT: Neoadjuvant chemotherapy; Ntx: Neurotoxicity; PT: Cisplatin/paclitaxel; QLQ: Quality of Life Questionnaire; QOL: Quality of life.

Table 2

Phase III clinical trials of recurrent ovarian cancer with quality-of-life measurement from 2003 to 2011.

Trial	QOL measure	Primary trial outcome	QOL outcome	Ref.
Interval secondary cytoreduction (GOG 152)	FACT-0	Interval cytoreduction provided no additional benefit	Baseline FACT-0 scores were significantly associated with OS but not PFS; less neurotoxicity in patients who did undergo cytoreduction	[8]
PLD and carboplatin compared with CT for platinum-sensitive ovarian cancer in late relapse	EORTC QLQ-C30 and -OV28	PLD and carboplatin showed superior PFS and better therapeutic index	Ongoing analysis of QOL	[14]
Nonplatinum topotecan combinations vs topotecan alone for recurrent ovarian cancer	EORTC QLQ-C30 and -OV28	Nonplatinum topotecan advantages do not provide survival advantage over topotecan alone	QOL did not change throughout the study and did not differ between treatment groups at baseline after the third cycle and after completion of the last cycle of chemotherapy	[15]
Gemcitabine vs PLD in progressive or recurrent ovarian cancer	EORTC QLQ-C30	No advantage of gemcitabine over PLD but should be considered in the spectrum of drugs	No statistically significant differences in QOL scores at baseline; however, QOL scores higher in first and second post-baseline QOL assessment; PLD patients had better scores in physical and emotional functions and in fatigue	[66]
Gemcitabine compared with PLD in platinum-resistant ovarian cancer	FACT-0	Gemcitabine may be an acceptable alternative to PLD	FACT-0 scores were not significant predictors of PFS; however, they were predictive of OS	[67]
Early vs delayed treatment of relapsed ovarian cancer	EORTC QLQ-C30	No evidence for survival benefit in early treatment based on CA-125	Median time-to-QOL deterioration shorter in early treatment group; significant disadvantages in role, emotional, social and fatigue subscales	[16]
CG vs carboplaltin in platinum- sensitive recurrent ovarian cancer	EORTC QLQ-C30 and -OV28	The addition of gemcitabine improved PFS and response rate	No statistically significant treatment differences for baseline scores between arms as well as for score changes from baseline to treatment discontinuation	[68]

CG: Carboplatin/gemcitabine; CT: Carboplatin/paclitaxel; EORTC: European Organization for Research and Treatment of Cancer: FACT-O: Functional Assessment of Cancer Therapy – Ovarian: OS: Overall survival: PFS: Progression-free survival: PLD: Pegylated liposomal doxorubicin: QLQ: Quality of Life Questionnaire: QOL: Quality of life.

Table 3

Common toxicity criteria data versus patient-reported data.

Side effect	Patient graded higher (%)	Physician graded higher (%)	Exact agreement (%)
Cycle #3			
Nausea	16	28	55
Emesis	9	14	78
Pain	32	14	54
Constipation	24	15	61
Dyspnea	34	5	61
Cycle #6			
Nausea	17	23	61
Emesis	9	10	81
Pain	32	11	51
Constipation	22	12	66
Dyspnea	40	5	55

Data taken from [12].