Introduction

Conventional endpoints such as survival, time to progression, and response rate have long been the foundation for cancer research, specifically in ovarian cancer. With advances in medical, surgical, and pharmaceutical treatment of ovarian cancer, additional endpoints are now emerging as important aspects of patient care. Quality of life and, more specifically, health-related quality of life (HRQOL), address important aspects of the patient’s life including physical, social, psychological, financial, and sexual issues, as well as the side effects of the chemotherapeutic medications that we rely on for treatment.

While functional status and quality of life have been quantified in oncologic practice since the advent of the clinical scale developed by Karnofsky and Burchenal in 1949, interest has increased over the past two decades in the systematic assessment of HRQOL through the use of standardized, self-administered measures for cancer patients, and these measures have become an important focus of benefit for newer treatment regimens. HRQOL assessment is a key factor in evaluating cancer burden and the effects of treatment. HRQOL assessment of women with ovarian cancer has been implemented into patient care in most trials by the Gynecologic Oncology Group (GOG) and is being adapted to standard of care. The benefits of using HRQOL assessment include better patient-caregiver communication and overall improvement of the quality of life.

Background: Ovarian cancer and its management interventions can produce significant impairments in health-related quality of life (HRQOL). These effects have been studied in both localized and advanced disease settings.

Methods: The authors assessed research reports that focus on the evaluation of HRQOL in patients with ovarian cancer in order to describe the findings and to suggest approaches that might maintain or maximize the quality of life in these patients.

Results: Evaluation of quality of life and functional impairment can include consideration of several issues such as the effects of the disease and its treatments on symptomatology, systemic therapy effects, the balance between life-prolonging but toxic protocols, and the sexual, psychosocial, social, and financial effects of treatment. The Gynecologic Oncology Group is actively studying these issues in its protocols.

Conclusions: HRQOL evaluation is a valuable measure in optimizing care of patients with ovarian cancer; but more research is needed to make such evaluations sufficiently inexpensive and easy to perform so that they can be more fully incorporated into general oncologic practice.
This article attempts to demonstrate that to achieve optimal treatment of ovarian cancer, HRQOL must be reviewed regularly in patients who are undergoing traditional medical, surgical, and chemotherapeutic treatments.

Discussion

The concept of quality of life as a normative criterion began in the period after World War II, promoted by technological advances in medicine and the culture of peace. In that regard, the phrase health-related quality of life covers those health-related aspects of life that are capable of being modified by the provision of health care. Globally, the concepts of good health, satisfaction with life, gainful employment, adequate shelter and housing, safety of one’s family, availability of education, leisure pursuits, and overall happiness incorporate most attributes to this overall notion. One author defined HRQOL as “the extent to which one’s usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment,” which incorporates both subjectivity and multidimensionality to the definition of HRQOL. With this in mind, a working definition that can be used in patients with cancer was proposed by Gotay et al as follows: “Quality of life is a state of well being which is a composite of two components: the ability to perform everyday activities which reflects physical, psychological, and social well-being and the patient’s satisfaction with the level of functioning and the control of disease and/or treatment-related symptoms.”

Specific measures to evaluate the outcome of an illness or its treatment include quantity or length of survival (conventional endpoints such as survival, time to progression, and response rate), quality of life, and economic costs. Although length of survival was previously considered the most important among these, the impact of illness on HRQOL has received increasing recognition. As a mainstream example, improvement in quality of life is one of two potential benefits that are considered by the US Food and Drug Administration for the approval of new anticancer drugs.

Industrialized societies, such as the United States, place the highest value on preserving and maximizing quality of life. Following a diagnosis of cancer, patients and their families may experience many emotions. After passing through the expected stages of bereavement extensively described by Kübler-Ross in the 1960s, the patient and family eventually accept the diagnosis. For dying patients, it is most important to improve quality of life and relieve suffering. The dilemma faced by patients and their family members is as difficult as the diagnosis; they not only must hold onto hope for a cure, but also need to make a decision to continue aggressive treatment vs palliative care. This decision is often made based on anticipated quality of life expectations. Interdisciplinary teamwork is vital to ensure that every patient’s needs are fulfilled and a holistic approach to the patient and family is maintained. Patient comfort and control of cancer-related symptoms can optimize the patient’s limited remaining time with family and friends.

Although many developments have occurred in the prevention, diagnosis, treatment, and risk of recurrence of cancer, death from this disease is still common. According to the American Cancer Society, approximately 270,290 women died of cancer in 2010, with 5% due to ovarian cancer. Despite advances in diagnostic techniques and therapy, cancer of the ovary is the most malignant cancer in women, where it is the fifth leading cause of cancer-related death. An estimated 21,550 new cases are diagnosed annually in the United States alone. Therefore, it remains the gynecologic malignancy of greatest concern in industrialized countries.

Surgery establishes the diagnosis, assesses the extent of disease, and aims for optimal cytoreduction. However, only a marginal number of patients present early enough for complete removal of the tumor in order to be successful in curing disease. A total of 80% of women with ovarian malignancy present with advanced-stage disease. Thus, surgery with chemotherapy is the primary treatment for the majority of women with ovarian cancer. Fortunately, advances in surgical and chemotherapeutic management have improved overall survival, with 45% of women of all stages surviving 5 years or longer. The median overall survival for patients with advanced ovarian cancer (FIGO stages II–IV) who were randomized to paclitaxel/platinum-containing chemotherapy in three large studies ranged between 36 to 39 months. Compared with historical data, this represents a median survival time that is six to seven times longer than that achieved after surgery alone. However, the disease and its treatment have considerable effects on the quality of life of patients with this cancer.

Traditional side effects of ovarian cancer include weight loss, bloating and ascites, fatigue, and pain. Side effects of treatment include neutropenia, weight loss, body distortion, fatigue, neuropathy, hair loss, sexual dysfunction, bowel and bladder incontinence, loss of taste and appetite, poor sleep, edema, and diminished mobility. An additional burden involves the amount of time receiving treatment that is lost from family and work. The combined effects of these factors—chemotherapy, physical impairment and mobility issues, psychological and emotional problems, social and financial difficulties, and sexual issues—contribute to diminished HRQOL.

Chemotherapy

Two classes of cytotoxic agents, the platinum and the taxanes, are key components of chemotherapy regimens for advanced disease. These two classes of agents carry with them entire spectrums of side effects that often significantly affect a patient’s quality of life. The clinical benefit in terms of median overall and progression-free
survival of combining paclitaxel rather than an alkylating agent with a platinum compound in stage III–IV\textsuperscript{17} or stage IIB–IV\textsuperscript{18} disease has been shown in first-line studies in a total of 1,057 women. Further data from three major studies in a total of 1,798 patients show enhancement of this benefit via improved overall tolerability when cisplatin is replaced by carboplatin.\textsuperscript{19,21} Of particular interest is a study by Lakusta et al\textsuperscript{22} involving a chart review of 60 women with ovarian cancer undergoing chemotherapy with platinum agents. Analysis of questionnaire responses from these patients was used to relate biomedical variables to HCQOL outcomes and to compare patients receiving cisplatin as first-line therapy with those receiving palliative carboplatin for recurrent disease. Women receiving first-line cisplatin reported more appetite disturbance, diarrhea, and nausea than those on palliative carboplatin. Most notably, HCQOL declined over time in the newly diagnosed patients, whereas improvements were noted in those with recurrent disease. Also in this study, lower HCQOL was found to predict death within 12 months of starting treatment.\textsuperscript{23}

In cases where different drugs show similar survival benefit in advanced malignant disease, issues relating to toxicity and quality of life — neurotoxicity, alopecia, neutropenia, myelosuppression, stomatitis, fatigue, and nausea — become increasingly important. For example, despite similarities in chemical structure and mode of action, docetaxel and paclitaxel cannot be regarded as having the same properties when used clinically. Most patients with ovarian cancer receive paclitaxel as a 3-hour infusion, whereas docetaxel is given over 1 hour. This shortened infusion time suggests a potential advantage in terms of patient convenience and factors such as clinic time and resources. Study results have shown that substituting docetaxel for paclitaxel in a platinum-based doublet does not compromise efficacy but may confer benefits in terms of toxicity and convenience for patients. When establishing a treatment plan for individual patients, risks and benefits must be balanced to ensure that the quality of time remaining is optimal.

Many studies have been performed to find the least toxic combination of medications used in chemotherapy for ovarian cancer in hopes of improving treatment tolerability and thus quality of life.\textsuperscript{23} Often the dose-limiting toxicity of the taxanes is neutropenia or, more specifically, febrile neutropenia.\textsuperscript{24} In addition, the promise of similar antitumor activity with reduced toxicity (neurotoxicity, ototoxicity, nephrotoxicity, and gastrointestinal toxicity) when carboplatin is used in place of cisplatin with a taxane has prompted researchers to explore combinations of many drugs for treatment.

Concerns have been raised regarding the neurotoxicity associated with combinations of paclitaxel with carboplatin. For example, a first-line therapy in 139 patients treated with a range of combination dosages of carboplatin plus docetaxel yielded an overall response rate of 66% and a median progression-free survival of 16.6 months, with extremely low levels of neurotoxicity. In addition, comparative data from a phase III study by the Scottish Gynecological Cancer Trials Group (the SCOTROC trial) involving 1,077 chemotherapy-naïve patients indicated that paclitaxel plus docetaxel has comparable efficacy and tolerability.\textsuperscript{25,26} In addition, three key comparative trials of paclitaxel-cisplatin vs paclitaxel-carboplatin — the Dutch-Danish trial, the GOG 158 study, and the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) trial — reported similar efficacy for both combination regimens in patients with advanced ovarian cancer but less neurotoxicity with carboplatin than with cisplatin.\textsuperscript{23} The severity and frequency of peripheral neuropathy with paclitaxel may be related to infusion times as well as dose, with more rapid infusions being associated with higher incidences. Thus, all of these factors, including patient time and side effects, need be included in HRQOL assessments.

Recently the use of intraperitoneal therapy has become more widely used. A GOG randomized phase III trial (GOG 172) in optimal stage III epithelial ovarian cancer showed that intravenous paclitaxel plus intraperitoneal cisplatin plus paclitaxel significantly lengthened progression-free and overall survival compared with intravenous paclitaxel plus cisplatin. A recent study in which 415 women with ovarian cancer were enrolled reviewed HRQOL effects of intraperitoneal vs intravenous treatment.\textsuperscript{27} The authors concluded that during active treatment, patients on the intraperitoneal arm experienced more HRQOL disruption, abdominal discomfort, and neurotoxicity compared with patients receiving conventional intravenous therapy. However, neurotoxicity remained significantly greater for intraperitoneal patients 12 months after treatment. This trade-off effect should be considered when discussing treatment options with patients. Future studies to mitigate the added burden associated with intraperitoneal therapy is ongoing.\textsuperscript{27}

Guidelines are in place to aid clinicians in the use of colony-stimulating factors in patients likely to be at risk of myelosuppression. One would expect that appropriate treatment of this type would minimize the incidence and severity of neutropenia in patients receiving docetaxel with carboplatin in future studies. In general, the proportion of patients experiencing grade III–IV nonhematologic adverse events such as arthralgia, myalgia, diarrhea, hypersensitivity, and fluid retention remains below 10% when premedication is administered with the taxanes as recommended.\textsuperscript{23} Also, the use of bevacizumab to palliate symptomatic ascites in patients with refractory ovarian carcinoma has been reported.

**Physical and Mobility Issues**
All patients suffering from physical and mobility problems related to cancer and treatment should be evaluated by physical therapy and rehabilitation medicine with an
early consultation. Even preoperative evaluation may be beneficial to prepare for the postoperative physical limitations and the specific interventions that will be employed. Two relevant physical limitations in ovarian cancer requiring physical rehabilitation are (1) prolonged bed rest from hospitalization and surgery and (2) the potential for lymphedema after staging surgery. For patients with advanced cancer, interventions are useful for maintaining mobility, improving stamina, decreasing fatigue, and retaining control over activities of daily living.

**Psychological and Emotional Problems**

Not surprisingly, psychosocial problems such as anxiety, depression, marital/partner difficulties, and interpersonal communication issues occur frequently in patients with cancer and tend to fluctuate with the clinical course of the illness. Patients generally experience the most difficulty at diagnosis, at recurrence, and with approaching mortality. Assessment of patient needs should occur at these times and also during more stable periods. Clinically significant depression and anxiety, assessed with the Center for Epidemiologic Studies Depression scale and State Anxiety subscale of the Spielberger State-Trait Anxiety Inventory, were found to be more prevalent than expected in cancer patients. Clinical depression was reported in 21% of patients, while 29% scored above the 75th percentile for anxiety. A standardized HRQOL form with each visit can track these issues and help to recognize the need for interventions. Psychological distress should be managed with appropriate counseling, support groups, medications (eg, antidepressants, anxiolytics), and referral to mental health professionals who have experience in working with cancer patients.

**Social and Financial Difficulties**

Economics and the availability of a personal support system also need to be evaluated. As a patient’s functional status declines, additional assistance may be required at home, and it is important to know when referral to a home care agency might be helpful. Community services that are often available are individual family and/or group psychological counseling, transportation, assistance with meals and household chores, and nursing care. Early involvement of a social worker is usually the most appropriate step in evaluating a patient’s supportive care needs and in determining appropriate resources. One recent study concluded that ovarian cancer patients may compensate for decreased HRQOL in physical, functional, and emotional areas with increased social support.

Financial burden also plays a role in cancer-related quality of life issues. A major impact of chronic illness is the inability to continue working, thus leading to possible job loss. Health insurance benefits in the United States are often linked to employment. In addition, cancer is usually considered an excluded preexisting condition, although new legislation makes it illegal to bar someone from insurance because of a preexisting condition. The Federal Rehabilitation Act of 1973 provides some protection for patients, and a number of states have legislation that protects the employment rights of these individuals, especially in relation to hiring discrimination and reasonable accommodation during needed treatments. The Americans with Disabilities Act of 1991 now provides federal protection to cancer patients. According to these acts, employers must accommodate patients receiving cancer treatment by allowing changes in schedules or workloads. Vocational counseling should be considered for individuals who lose their jobs or who are unable to continue in their previous employment secondary to the effects of cancer and/or its treatment.

**Sexual Issues**

Cancer and cancer treatment can exacerbate old sexual function problems and can also create new ones. As sexual dysfunction is prevalent in healthy individuals, these issues can often be overlooked initially. As a first step, oncologists should review the patient’s present level of sexual activity and discuss the potential impact of therapy prior to initiation. Awareness of these potential problems will help the patient adapt to posttreatment difficulties such as fatigue from radiation and chemotherapy, and body image distortion by weight loss, hair loss, and physical scars that can make patients feel less sexually attractive. In addition, sexual dysfunction, decreased libido, and vaginal dryness can be precipitated by enervation damage from abdominal and pelvic surgical procedures, removal of tissues important for sexual activity with resultant functional impairment in surgical procedures (eg, vaginectomy, radical vulvectomy), premature menopause, and estrogen deficiency. A pretreatment discussion of sexuality and intimacy provides a baseline for comparison during subsequent reevaluation after treatment.

**Assessment of Individual Perceptions of Quality of Life**

A complex relationship exists between treatment efficacy and toxicity. Since quality of life is a subjective appraisal of the impact of illness and treatment on the patient’s life, individual responses can vary widely among people with the same objective status of health relative to the points discussed above. These disparities have led to the need to evaluate quality of life from the individual patient’s viewpoint rather than from the health care provider’s viewpoint.

Several validated and reliable questionnaires are available for assessment of quality of life. To measure HRQOL specifically, multiple questionnaires are available that have been evaluated. These questionnaires can be generic health status questionnaires that are applicable to all populations and can be completed by individuals both with and without medical illness, or they can be generic illness instruments that are applicable to popu-
lalations with any medical illness or condition. They can be used to compare different illnesses, levels of disease severity, or types of interventions; or they can be disease-specific questionnaires.

The GOG has begun implementing different HRQOL measurements in its study designs for ovarian cancer. HRQOL was measured using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire. The FACT-O is a multidimensional questionnaire developed and validated for use by ovarian cancer patients. It includes the 27-item FACT-General (FACT-G version 4) questionnaire targeted toward general cancer patients and includes 12 questions specific to issues faced by ovarian cancer patients (FACT-O subscale). The FACT-G version 4 questionnaire includes the following four subscales: (1) physical well-being (PWB; 7 items), (2) social well-being (7 items), (3) emotional well-being (6 items), and (4) functional well-being (FWB; 7 items). These subscales can be analyzed separately or aggregated to produce a total HRQOL score.27 The FACT-G has demonstrated reliability, validity, and responsiveness to change over time.31 Two of the FACT-G subscales (PWB and FWB) plus the FACT-O subscale can be combined to represent the Trial Outcome Index. This index has excellent psychometric properties, including internal consistency and test-retest reliability,32 and sensitivity to change over time in ovarian cancer patients responding to platinum-taxane therapy.33 Where HRQOL data can be particularly useful in interpreting treatment implications. Overall HRQOL disruption was largely captured by the FACT-O Trial Outcome Index, which is a summation of physical and functional well-being subscales. Higher FACT-O scores are associated with better HRQOL.

Another example is the Patient-Reported Outcomes Measurement Information System (PROMIS), a network of primary research sites and coordinating centers that work collaboratively to develop a series of dynamic tools in order to reliably and reliably measure patient-reported outcomes. Funded by the National Institutes of Health, PROMIS provides an opportunity to improve health care outcomes by giving decision makers hard data on how health care affects what patients are able to do and how they feel. PROMIS has a specific framework for cancer patients that is also being developed.34,35 PROMIS was developed with the input of hundreds of people with a wide variety of medical conditions, the health care providers who treat them, members of the general population, and extensive literature reviews. The framework is divided into physical, mental and social health. Each of these major domains encompasses multiple subdomains (e.g., the mental health domain focuses on emotional distress, cognitive functioning, and positive psychological functioning). These subdomains are further divided (e.g., emotional distress comprises anxiety, depression, anger, substance abuse, and the negative impact of illness). An important component of all the dimensions is the respondent’s level of satisfaction with the specific outcome.35

Utilization of HRQOL data is useful in many ways, despite the format from which we extrapolate it, FACT-O or PROMIS-Cancer (PROMIS-Ca). It not only will encourage communication between the patient and practitioner to provide treatment that is in line with the patient's overall wishes for HRQOL, but also can be used clinically. An HRQOL analysis can serve as one means of determining overall clinical benefit, particularly when treatment-related side effects are considerable. Compared to the control therapy, the alternative treatment option may be associated with a variety of combinations of relative survival benefit and HRQOL. Outcomes can be grouped into categories based on length of survival with better or inferior HRQOL. Improved HRQOL during therapy may outweigh somewhat shorter survival duration.

There are multiple other potential benefits in studying HRQOL. Data can be utilized from earlier treatment regimens and can be developed as a future planning tool for assessing the need for further treatment, rehabilitation, or palliative care. In particular, HRQOL assessment may reveal anxiety or depressive symptoms or a complaint of pain or dyspnea that may initiate patient-physician communication about medical, psychological, or social interventions to improve the patient's well-being.36,37 Two recent studies demonstrated that routinely providing HRQOL information to oncologists can improve patient-physician communication.37,38 Another study demonstrated that a large proportion of women with FACT-O scores in the lowest quartile reported problems that potentially were amenable to clinical interventions such as symptom management and psychosocial support.39 HRQOL surveys provide the opportunity to utilize patient-reported issues to guide individual clinical care. For instance, a brief multidimensional HRQOL instrument might be administered at every chemotherapy and office visit. Significant changes can be flagged for follow-up and could potentially identify a problem that may not have been reported by the patient during the visit. Even more beneficial would be a standardized computer-generated printout of HRQOL scores that could plot a comparison to monitor treatment objectives. It is likely that most patients would claim that weekly assessment would aid in focusing discussions with their health care team and that providers would find changes in patient responses over time to be useful in treatment strategy.

Challenges in HRQOL use and interpretation exist in all disciplines. The identification of what constitutes clinically significant differences and meaningful changes in HRQOL, the development and testing of conceptual models linking medical and psychological variables to HRQOL,40 and the development of item banks and standardized computer tools to measure HRQOL in a way that permits comparison across diseases and treatments have yet to be completely established. Implementation
by the GOG of the FACT-O Trial Outcome Index and PROMIS-Ca in many of its study protocols is a productive step in addressing the challenges that come with a nonstandardized approach of reporting data in such a broad topic as HRQOL. However, such implementation is not yet universal throughout gynecologic oncology practice and ovarian cancer.

A second challenge will be in defining when a clinically meaningful change in the HRQOL data warrants a treatment modification by the physician. For example, when interventions based on HRQOL are meaningful and important to the patient but not statistically significant in a scientific community, how does the health care team construct treatment plans on an individualized basis yet still maintain a level of standard of care in a community based on strict evidence? With HRQOL data combined with statistics regarding disease stage and severity, treatment status, progression-free survival, and performance status, as well as psychological, social, cultural, and economic issues, one can ascertain that evaluation of these interrelationships is critical to an understanding of what influences HRQOL and the potential for modifying these factors through targeted interventions.

Conclusions
Quality of life is composed of broad concepts that affect global life satisfaction. HRQOL has been defined for matters related to health and illness. Multiple validated and reliable questionnaires are available for assessment of HRQOL, including generic health status instruments, generic illness instruments, disease-specific instruments, and combined instruments such as the FACT-O and the PROMIS-Ca.

HRQOL assessment plays an important role in medical care, and this is especially significant in ovarian cancer treatment as 80% of newly diagnosed patients present with advanced disease and require extensive surgical and chemotherapeutic treatment regimens that are associated with significant morbidity. HRQOL data can be utilized in clinical trials, with an endpoint of improvement of HRQOL. The data can also be used as a tool in standardizing the efficacy and tolerability of treatment. In addition, information from the HRQOL assessments may help identify the need for changes in treatment regimens that may have otherwise been overlooked and can aid in the deciding when to pursue need for further treatment vs palliative care.

Prolongation of life, without regard for the quality of that life, is not a universally desired goal. When considering aggressive, life-prolonging treatments and end-of-life decisions, it is necessary to consider each individual’s assessment of what makes life worth living. Overall HRQOL assessment can help patients with ovarian cancer maintain autonomy when faced with the difficult decision between aggressive, life-prolonging treatments vs end-of-life decisions. As medical, pharmaceutical, and surgical techniques continue to prolong life much longer than our predecessors would have imagined, it is now the role of today’s physicians to encompass quality of life into their ever-changing role as health care providers and patient advocates. To reach such positive outcomes, the use of an interdisciplinary treatment team approach is vital to each patient’s needs. To optimize treatment decisions for patients with ovarian cancer, clinicians need to be familiar with differences between regimens in terms of toxicity, dosage, and administration, and emerging data from HRQOL assessments.

References