Quality of Life Research in Endometrial Cancer

What Is Needed to Advance Progress in This Disease Site? Methodological Considerations From the Gynecologic Cancer InterGroup Symptom Benefit Working Group Brainstorming Session, Leiden 2012

Jessica N. McAlpine, MD, Elfriede Greimel, PhD,† Lori A. Brotto, PhD,* Remy A. Nout, MD, PhD,‡ Emad Shash, MD,§ Elisabeth Åvall-Lundqvist, MD,|| Michael L. Friedlander, MBChB, FRACP, PhD,¶ Florence Joly, MD,# and on behalf of the Gynecologic Cancer InterGroup (GCIG)*

Background: Quality of life (QoL) in endometrial cancer (EC) is understudied. Incorporation of QoL questionnaires and patient-reported outcomes in clinical trials has been inconsistent, and the tools and interpretation of these measures are unfamiliar to most practitioners. In 2012, the Gynecologic Cancer InterGroup Symptom Benefit Working Group convened for a brainstorming collaborative session to address deficiencies and work toward improving the quality and quantity of QoL research in women with EC.

Methods: Through literature review and international expert contributions, we compiled a comprehensive appraisal of current generic and disease site–specific QoL assessment tools, strengths and weaknesses of these measures, assessment of sexual health, statistical considerations, and an exploration of the unique array of histopathologic and clinical factors that may influence QoL outcomes in women with EC.

Results: This collaborative composition is the first publication specific to EC that addresses methodology in QoL research and the components necessary to achieve high quality QoL data in clinical trials. Future recommendations regarding (1) the incorporation of patient-reported outcomes in all clinical trials in EC, (2) definition of an a priori hypothesis, (3) utilization of validated tools and consideration of new tools corresponding to new therapies or specific symptoms, (4) publication within the same time frame as clinical outcome data, and (5) attempt to correct for disease site–specific potential confounders are presented.

Conclusions: Improved understanding of methodology in QoL research and an increased undertaking of EC-specific QoL research in clinical trials are imperative if we are to improve outcomes in women with EC.

Key Words: Quality of life, Clinical trials, Endometrial cancer, Patient-reported outcomes, Sexual health

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*Department of Gynecology and Obstetrics, University of British Columbia, Vancouver, British Columbia, Canada; †Department of Medical Psychology and Psychotherapy, Medical University of Graz, Graz, Austria; ‡Department of Clinical Oncology, Leiden University Medical Center, Leiden, the Netherlands; §EORTC, Brussels, Belgium; ||Department of Gynecologic Oncology, Karolinska University Hospital, Stockholm, Sweden; ¶Department of Medical Oncology, The Prince of Wales Hospital, University of New South Wales Clinical School, Sydney, Australia; and #Departments of Medical Oncology and Clinical Research, Centre Francois Baclesse, CHU Côte de Nacre, University of Basse Normandie, Caen, France.

Address correspondence and reprint requests to Jessica McAlpine, MD, Division of Gynecologic Oncology, Department of Gynecology and Obstetrics, University of British Columbia, 6th floor, 2775 Laurel St, Vancouver, British Columbia V5Z-1M9, Canada. E-mail: jessica.mcalpine@vch.ca.

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Endometrial cancer (EC) is the fourth most common cancer in women in developed countries and is increasing globally.[1,2] Most women with EC have early-stage disease and enjoy long survival, making health-related quality-of-life (QoL) issues of paramount importance. Endometrial cancer has many associated health factors that can influence QoL such as obesity, advanced age, and medical comorbidities,[3–5] which are often not accounted for in data analyses or interpretation. Although improving, the quantity and quality of QoL data pertaining to women with ECs lag behind other malignancies (eg, breast, prostate cancer) and have not been prioritized in the development of new trials in this disease.[6,7]

There are many challenges in the collection and reporting of QoL data across all disease diagnoses. Standards for analysis of QoL data and symptom control are poor, and practice varies greatly. Results of randomized control trials are almost always framed with emphasis on survival differences or response rates for primary outcomes with less than a quarter of randomized control trials defining symptom control or QoL as a primary outcome.[6,8] The QoL data may be found only in the appendix/supplementary reports of the study, may be published at a later date, or commonly are not published at all.[8] This mind-set has to change as what in the past we have considered adequate surrogates; toxicity scores, or clinician-recorded adverse effects, may miss or dramatically underestimate patient symptoms.[9,10] Quality-of-life instruments were not intended to be symptom instruments although they do contain symptom items and are more representative of patient experience than physician impression. Patients are playing an increasing role in determining which treatment they receive,[11,12] and choice may be contingent on QoL concerns; hence, the measurement and accurate interpretation of these are essential.[13]

In the last 2 decades, it is recognized that assessment of patient-reported outcomes (PROs) may provide the best reflection of treatment-related or disease-related adverse effects.[14–18] Regulatory authorities in both the United States and Europe now consider PROs data in support of drug labeling claims. Patient-reported outcomes can inform clinical decision making for an individual and can be used to guide research and health policy for the general population. In March of 2012, the Center for Medical Technology Policy published recommendations for incorporating PROs in clinical comparative effectiveness research in adult oncology.[19] More recently still, at the end of February 2013, the Consolidated Standards of Reporting Trials group published 5 checklist items recommended for randomized controlled trials reporting PROs.[20] Future publications or funding will be impossible without investigators demonstrating dramatic improvement in exploring these realms.

The Gynecologic Cancer InterGroup (GCIG), inclusive of 24 clinical trial groups representing over 20 countries, wishes to promote these changes in the design of future trials in EC. In December of 2012, GCIG members of the Symptom Benefit Working Group met and initiated a course of action pertaining to the inclusion of high-quality QoL research in EC trials. This study, and the accompanying GCIG publication in this journal, serves as a communication of the current state of the art in this disease, what is missing, available tools/resources, and analytical considerations that are essential to obtaining critical QoL data that can inform and direct treatments for women with EC.

METHODOLOGICAL CONSIDERATIONS

Types of Quality-of-Life Measures

Generic instruments are designed to assess broad aspects of subjective health. These instruments are potentially suitable for a wide range of patients with chronic disease as well as for the general population. Such instruments allow for comparisons of results across studies of different patient populations, but their disadvantages are that they are less responsive to clinically important changes in health status. A well-known and widely used generic instrument is the SF-36.[21] There are no EC-specific items; however, it can be applied to study EC survivors, comparing QoL parameters to the general population, as in the postoperative radiation therapy in endometrial carcinoma 1 long-term QoL analysis.

General cancer instruments are designed for use in specific disease populations. Validated instruments are available to assess the QoL of patients with cancer including all gynecologic cancer sites. The most widely used instruments are the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-30) and the Functional Assessment of Cancer Therapy General (FACT-G) measurement system.[22,23]

Cancer site–specific instruments are designed to measure QoL issues that are affected by a specific cancer site. Cancer site–specific modules are often used as supplements to more general questionnaires. The combination of a general questionnaire with cancer site–specific scales has become the standard approach to QoL measurement in clinical trials. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer24 (EORTC QLQ-24) and Functional Assessment of Cancer Therapy-Endometrial (FACT-EN) are examples of site-specific modules in EC.[23,24]

A variety of symptom assessment scales including symptoms associated with gynecologic cancer may also be useful.[25–28] However, symptom assessment tools are not intended to be QoL instruments because symptoms contribute to, but do not determine, QoL. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) has been the standard source of adverse symptom data reported by clinicians. Recently, patient self-reporting has been proposed, and the CTCAE for common symptoms was adapted into a web-based patient-reporting system that has been tested in patients with gynecologic malignancies[29,30] with the goal of capturing specific symptoms intensity, frequency, and duration and how this influences daily activity. The PRO CTCAE version may be a useful tool but needs additional assessment in clinical trial settings.[30–32]

EORTC QLQ-C30 and EORTC QLQ-EN24

The EORTC QLQ-C30, available in 86 languages, was designed for the assessment of QoL of patients with cancer. The questionnaire contains 30 questions belonging to 5 functional scales, 9 symptom scales, a scale concerning financial

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TABLE 1. Comparison of FACT-G and the EORTC QLQ-C30

FACT-G		EORTC QLQ-C30	
Physical	Energy	**Physical**	Strenuous activity
	Nausea		Long walk
	Family needs		Short walk
	Pain		Stay in chair
	Side effects		Self-care
	Feel ill		
	Bedridden		
Social/family	Close to friends	**Social**	Interfere with family life
	Family support		With social activities
	Friends' support		
	Family comm. illness		
	Close to partner		
	Sexual life		
Emotional	Feel sad	**Emotional**	Tense
	Satisfied with coping		Worry
	Losing hope		Irritable
	Feel nervous		Depressed
	Worry/dying	**Cognitive**	Concentration
	Worry/getting worse		Remembering
Functional	Able to work	**Role**	Limited work
	Work fulfilling		Limited leisure
	Enjoy life		
	Sleep well		
	Enjoy pleasure		
	Content with QoL	**Overall**	Health
			QoL
Symptoms		Pain, fatigue, nausea, and vomiting	
		Dyspnea, sleep, appetite, constipation	
		Diarrhea	
Other scale		Financial difficulty	

difficulties, and 1 global health status/overall QoL scale (Table 1). Previous studies showed good reliability and validity for different cancer diagnoses.[22,33–35] The EORTC QLQ-EN24 was designed for patients with all stages of EC treated with pelvic surgery, chemotherapy, radiotherapy, or concomitant radio/chemotherapy. Available in 11 languages, it can be used as a supplement to the EORTC QLQ-C30 for clinical trials.[24] The module consists of 24 questions and 6 subscales as follows: lymphedema, urological symptoms, gastrointestinal symptoms, body image, sexual function, and vaginal symptoms. The module was developed and validated in multicultural setting within the EORTC QoL Group including patients and health care professionals.

FACT-G and FACT-EN

The FACT-G was developed as a general measure for QoL of patients with cancer. The instrument contains 4 domains and 27 questions: physical well-being, social/family well-being, emotional well-being, and functional well-being.[36,37] Each question has 5 options. All item scores are recoded to make a high score corresponding to better QoL. An EC-specific scale (FACT-EN) was developed including 16 questions comprised in 1 domain. FACT-EN has been utilized in several trials although the authors are not aware of a formal validation paper. In contrast, the FACT-G has been validated extensively in patients with different cancers[38–43] and is available in 60 languages.

Comparison of Scale Structures of the EORTC and Functional Assessment of Chronic Illness Therapy Systems in QOL Assessment

The comparison of the 2 sets of instruments is shown in Tables 1 and 2. The functional scales of the FACT-G and the EORTC QLQ-C30 both include physical, mental or

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emotional, social, and role or functional subscales and both have an overall measure for QoL; the FACT-G uses a summation of all scores, whereas the EORTC QLQ-C30 measures it separately. Direct comparison of these tools reveals differences in the social/family subscales but otherwise essentially equating results.[44] The FACT-EN and the EORTC QLQ-EN24 have no common subscales to compare but the overall content explored is similar.

Statistical Considerations

Considerations herein are not specific to EC trials, yet the lack of adherence to these principles in most QoL investigations warrants review. When designing a trial, careful consideration must be given to fundamental questions and defining an a priori hypothesis. What are the objectives of the trial, what are the expected symptoms or QoL end points of interest, and what do you expect to find? Once this has been decided, the appropriate QoL measure is needed.[45] Quality-of-life data including PROs end points should be incorporated into protocol development as early on as possible. Will the PROs data make a difference to the conclusion of the study? The answer to that question may depend on the clinical context of the trial. For interventions or disease sites where cure is possible, QoL may be an appropriate secondary end point with perhaps less influence on the determined "success" of the trial as compared with traditional survival/recurrence end points. If cure is not possible, such as is often the cases in recurrent EC, QOL may be the primary end point, focusing on relief or improvement of symptoms with the potential to completely alter the trials conclusions, or as another example, if running a noninferiority trial and treatment regimens are found to be equivalent, differences in PRO end points may be the main factor influencing selection for clinicians and patients. Increasingly, the option of "double primary" end points

TABLE 2. Comparison of FACT-EN and the EORTC QLQ-EN24

QLQ-EN24 Scales		FACT-EN (1 Scale)
		Stomach swelling/cramps/discomfort/pain, vaginal bleeding/discharge appearance, hot flashes, cold sweats night sweats, fatigue, painful intercourse, digesting food, short of breath, constipation, frequent urination, pelvic pain/discomfort
	Swelling in legs	
Lymphoedema	Heaviness in legs	
Urological symptoms	Urge to pass urine	
	Frequent urination	
	Leaking of urine	
Gastrointestinal symptoms	Pain/burning when passing urine	
	Urge to move bowels	
	Leakage of stools	
	Passing wind	
Body image problems	Cramps in abdomen	
	Bloated feeling	
	Feeling less attractive	
	Feeling less feminine	
Sexuality/vaginal symptoms	Sexual interest	
Symptoms	Sexual activity	
	Sexual enjoyment	
	Pain during sexual intercourse	
	Dry vagina	
	Short/tight vagina	
	Pain in back/pelvis	
	Tingling/numbness	
	Muscular pain	
	Hair loss	
	Taste change	

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that incorporate both PROs and a conventional end points may ensure QoL parameters, which are emphasized appropriately and satisfy study regulators.

When should data collection for QoL end points occur and for how long? A timed end point (eg, 6-week intervals) versus event-based intervals (eg, with each cycle of chemotherapy) would yield very different data in terms of symptoms experienced in EC patients receiving chemotherapy every 4 weeks. Different treatment arms within a trial may have different schedules, and careful consideration must be given to the timing of collection of PROs. Early versus late adverse effects must be distinguished and experience with treatment modalities, and disease course will help guide length of follow-up according to the research question posed.

Power calculation needs to be specific for the PRO end points. Numbers targeted for patient enrolment based on survival or other traditional outcome measures will not transfer to PROs data analysis but may help frame the realistic expectations to work within. Often, PROs are reported as a proportion of patients experiencing a change from baseline, and proper collection of baseline data is therefore essential. An excellent guide for the steps to analysis of health-related QoL data has been previously published.[46]

Management of missing data is a huge challenge in QoL trials. Missing data may result in loss of power to detect a change/difference and bias. A high proportion of missing data is preventable, but even when clinical trials are designed well, a multitude of logistical and administrative factors can interfere with QoL implementation and collection, particularly in series with long-term follow-up or very poor prognosis. To maximize questionnaire response rates, a well-organized method of collection is essential.[47] Study results from series with a significant portion of missing end points must be interpreted with caution, as the reasons for missed data may be nonrandom (eg, in patients with poor health who are less likely or unable to fill out questionnaires). Possible explanations include (1) lack of research staff or resources within a health center to execute trial as designed, (2) real or staff-perceived health status and "willingness" of the patient to complete questionnaires, and (3) lack of interest by clinicians or research staff. Despite 80% of health care professionals reporting that they believe that QoL information is valuable, less than 50% of clinicians implement QoL assessments in practice. Lack of familiarity with tools, data assessment, discomfort with topics, belief that little can be done to improve QoL concerns identified, and time/logistical concerns in busy clinics are commonly cited reasons for this. Repeatedly, it has been shown that patient refusal is the least frequent limiting factor in data collection.[48]

Standardized methods of reporting results are also essential as mere publication of questionnaire results or QoL scales may be uninterpretable or uninformative. Ultimately, PRO end points need to be shared either in the main study as survival/efficacy outcomes, as a companion paper in the same journal, or within the same time frame to have meaningful impact on decision making for patients and their medical team.

ASSESSMENT OF SEXUAL HEALTH

Sexual difficulties after treatment with gynecologic cancer affect between 30% and 100% of survivors and represent one of the most distressing long-term sequelae of cancer.[49] Because one's sexual health is inextricably linked to one's overall assessment of QoL, changes in sexual function can have a dramatic bearing on overall well-being. Specifically among EC survivors, a recent cohort study found that 89% scored below the diagnostic clinical cutoff for sexual dysfunction.[50]

Previous studies of sexual function in gynecologic cancer have tended to focus on end points such as sexual intercourse frequency, functional capacity, dryness, pain, and orgasm with intercourse.[51,52] One sexuality-specific measure not initially designed for survivors, the Female Sexual Function Index, has also been used among EC survivors and is reliable, valid, and sensitive to treatment.[53] Recent qualitative investigations illuminate that measures, which rely on intercourse frequency or intercourse-related parameters, may not capture the nuanced way in which survivors express their sexuality.[52] For example, one may have an increase in intercourse frequency for reasons totally unrelated to her interest/motivation for sex (eg, a wish to please a partner; to avoid conflict). Although the EORTC QLQ-C30 is the criterion standard measure of QoL among survivors, there is no sexual health component within it. QLQ-EN 24 does have sexual function scales; however, of the 6 items querying sexual function, questions apply only to within the past 4 weeks, only 1 item measures sexual desire, and 4 questions are applicable only if the patient has been sexually active with implied vaginal intercourse. Sexual desire is complex, and a single item assessing degree of desire may not capture a survivor's libido. To limit questions only to those survivors who are currently sexually active may lead to scores of missing data due to survivors' decisions about when best to reintroduce sexual activity after treatment.

To overcome these shortcomings, focus groups of survivors identify sexual self-esteem, sexual desire, body image, and relationship intimacy as key facets of sexuality that are not captured by existing measures.[54] This led to the development of the National Institute of Health Patient-Reported Outcomes Measurement Information System Sexual Function and Satisfaction (PROMIS SexSFFS) measure.

The 81-item PROMIS SexSFFS contains 11 domains in the areas of sexual interest, lubrication, vaginal discomfort, global satisfaction with sex life, sexual activities, orgasm, interfering factors, therapeutic aids, anal discomfort, screener questions, and 1 male-specific domain.[55] Subscales can be chosen based on the survivor population and end points of interest, is neutral to a participant's sexual orientation or partner status, and has been suggested to be useful for both clinical trial research as well as in clinical practice.

Although this instrument is relatively new, a number of advantages over existing self-report measures have been identified. First, the PROMIS SexFS was developed and validated among samples of cancer survivors, which improves the relevance of items to the way sexuality is experienced among survivors. To this end, items were derived from a conceptual model outlining the proposed mechanisms by

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TABLE 3. GCIG recommendations emerging from the 2012 symptom benefit working group sessions on QoL research in clinical trials in EC

(1) QoL data, with the essential inclusion of PROs, should be collected in all prospective phase III EC trials as primary or secondary outcome measures. This includes trials assessing first-line therapies, maintenance, treatment for recurrent disease, survivorship, and palliative care settings in low-risk, intermediate-risk, and high-risk EC patients.

(2) An a priori hypothesis is needed, defining the QoL research question and end point(s), with statistical consideration of differences in outcomes anticipated and consideration of how the data will be analyzed and presented.

(3) QoL data, patient symptoms, and PROs should be captured using validated tools. Consideration should be given to the use of generic or cancer-specific tools (or both), EORTC or FACT systems, symptom specific, sexual health, language, culture, scale structure, comparison groups as outlined in detail herein.

(4) PROs data should be published with or within the same time frame as other outcome data for all EC trials.

(5) Where possible, collection of and correction for possible confounders of QoL outcomes in EC patients should be undertaken. Body mass index, age, medical comorbidities, histology, and stage are examples of parameters that can influence decision making for surgery, chemotherapy, and radiation and may impact outcomes, including traditional survival parameters, toxicity, and PROs.

which cancer impacts sexuality.[54] Second, scales can be chosen and administered selectively based on the population and the expected domains of impact. During the validation process, the developers also established a brief version (8 items for women; 10 items for men) consisting of the 1 to 3 best items from each domain. Similar to findings using the existing criterion standard for measuring women's sexual function (the Female Sexual Function Index), the PROMIS SexFS also significantly predicted survivors who were interested in seeking professional treatment for their sexual concerns.

Limitations of the PROMIS SexFS include lack of items that measure vulvar discomfort, lack of cross-cultural validation, and applicability specific to EC patients, which specifically is uncertain because only a small component (15%) of the validation cohort had gynecologic cancers and the proportion of EC survivors within that cohort is unknown.

INTEGRATING CLINICOPATHOLOGIC PARAMETERS INTO CLINICAL TRIAL DESIGN: STEPS TO STRATIFYING WOMEN WITH EC BY PARAMETERS KNOWN TO INFLUENCE OUTCOMES

EC and Clinical Factors

How do age, obesity, and other comorbidities (eg, diabetes, hypertension) common in this population impact QoL parameters in EC patients? The GCIG accompanying study in this journal reviews trials in obese populations and assessment of treatment-related adverse effects, however, as yet we do not have a system to stratify the complex phenotypic differences in EC patients. Chemotherapy trials are seldom designed or powered to assess different clinical or demographic parameters of patients; however, it would be predicted that patients who are older, with preexisting comorbidities, may yield different PROs than their younger counterparts receiving the same treatment. There is less participation of the elderly in clinical trials, resulting in less QoL data available to assess. Outside of clinical trials, treatment in the elderly varies widely, even within a given cancer center. Multiple factors (renal function, Eastern Cooperative Oncology Group status, cardiac disease, prior chemotherapy/prior radiation, physician bias) may influence decision to proceed with surgery, surgical aggressiveness, choice of chemotherapy, number of agents, cycles given, or participation in clinical trials. In the future, it is hoped that accommodation and possible stratification for these factors would be part of clinical trial design. It seems unlikely that all women with EC should follow the exact same treatment algorithms, but what is "best" for an individual, both in terms of survival parameters and QoL, has yet to be determined.

EC and Histopathologic or Risk Group Subsets

The majority of QoL literature in EC patients comes from women with low-grade early-stage disease. Little is known about the symptoms of women with advanced-stage disease and/or high-risk histologic subtypes of EC. In these subgroups, surgery may be more extensive, and adjuvant chemotherapy and radiation are routinely recommended with subsequent impact on QoL. For long-term survivors of high-risk disease, data on QoL are strikingly deficient, and support/intervention studies are completely absent. Some of the new symptom-specific tools encompass QoL issues relevant to advanced disease EC patient populations (eg, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity and EORTC Quality of Life Questionnaire on Chemotherapy-Induced Peripheral Neuropathy 20 both assess chemotherapy-induced neuropathy) but are not specific to this disease site. Although prior trials in advanced-stage disease EC have focused on traditional survival end points with secondary or no QoL end points collected, the patient populations enrolled (even with lower numbers of women who survive long term) are available for surveys exploring survivorship needs. Data from these high-risk subgroups may provide a starting point in designing appropriate interventions and may inform and influence the design of future clinical trials.

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GCIG RECOMMENDATIONS

The GCIG Symptom Benefit Working Group respectfully submits the following recommendations pertaining to QoL research in clinical trials in EC (Table 3) with all participating trial groups asked to implement these recommendations by 2015. With adherence to these 5 items, we anticipate an improvement of the quality and quantity of QoL clinical trials in EC from the time of diagnosis until the end of life.

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For a complete list of references please contact Jessica McAlpine, MD. Email: Jessica.Mcalpine@vch.ca.

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