Chapter 9 |

The GOG Foundation, Inc. Patient Reported Outcomes


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The GOG Quality of Life (QOL) committee was formed in 1992 to evaluate phase III studies for their appropriateness for a QOL component, and to develop this component with the highest scientific rigor. Under the initial co-leadership of David Cella, PhD, and Donald Gallup, MD, from 1992 – 2004, this committee excelled, as evidenced by site visit review scores in the "Outstanding" to "Excellent" range. In 2004, the committee was chaired by Lari Wenzel, PhD, a psychologist with cancer patient-reported outcomes (PROs) expertise, and co-chaired by Jeffrey Bell, MD, a gynecologic oncologist. In 2011 David Cohn, MD, a gynecologic oncologist, joined as co-chair as the committee expanded goals to incorporate comparative and cost-effectiveness outcomes. Since the 2013 merger of three national cancer cooperative groups (NSABP, RTOG, GOG) into NRG Oncology, quality of life and patient-reported outcomes have been developed and evaluated under the Patient-Centered Outcomes Research (PCOR) committee, chaired by Benjamin Movsas, MD, with vice-chairs Patricia Ganz, MD, and Dr. Wenzel. The PCOR Committee works to assess and improve patient-centered outcomes in therapeutic and cancer control trials across NRG Oncology cancer disease site and non-disease site committees. This report provides an update on key accomplishments since the Gynecologic Oncology Group's (GOG) 43rd anniversary publication, specific to quality of life and patient-reported outcomes contributions within gynecologic oncology. The report highlights the following areas of QOL research emphasizing work published since 2013: (1) Quality of life and PROs in Gynecologic Cancer Clinical Trials; (2) Quality of Life and PROs in Symptom Assessment; and (3) Quality of Life and PROs as Outcome Prognosticators.

Quality of life and PROs in Gynecologic Cancer Clinical Trials

Phase III gynecologic cancer clinical trials have continued to include quality-of-life measures as secondary endpoints, with rigorous conceptual justification, measurement selection and well-powered statistical plans. For example, in two significant ovarian cancer trials , GOG-262 and GOG-213, select PROs were incorporated, which added to a comprehensive understanding of trial results. PROs, which included assessments of quality of life (FACT-O-TOI), neurotoxicity (FACT/GOG-NTX) and abdominal discomfort (FACT/GOG-AD) served as secondary endpoints in GOG-262, a trial designed to determine whether dose-dense weekly paclitaxel and carboplatin would prolong progression-free survival as compared with paclitaxel and carboplatin administered every three weeks among patients receiving and those not receiving bevacizumab. Patient-reported outcomes were analyzed for patients who underwent primary cytoreductive surgery followed by chemotherapy. Overall, weekly paclitaxel, as compared with paclitaxel administered every three weeks, did not prolong progression-free survival among patients with ovarian cancer. Further, patients who received weekly paclitaxel reported lower scores on the FACT-O TOI (reflecting lower quality of life) during the assessment period than did those who received paclitaxel every three weeks. The incidence of patient-reported neuropathy was similar in the two treatment groups, although the patient-reported severity of neuropathy was greater among those receiving weekly paclitaxel than among those receiving paclitaxel every three weeks, and that finding persisted throughout the study period. The quality-of-life scores among the 16% of patients who did not receive bevacizumab did not differ significantly between the two study groups.[1] GOG-213 illustrated the im-

portance of achieving longer survival intervals while retaining quality of life as a key goal when developing trials for patients with recurrent ovarian cancer. The results indicated that in this patient population with platinum-sensitive, recurrent ovarian cancer, secondary surgical cytoreduction followed by chemotherapy did not result in longer overall survival than chemotherapy alone. Moreover, quality of life decreased significantly after surgery, although it did not differ significantly between the two groups after recovery.[2]

Notable endometrial cancer clinical trials include that reported by Matei and colleagues, GOG-258 tested whether six months of platinum-based chemotherapy plus radiation therapy (chemoradiotherapy) was associated with longer relapse-free survival (primary end point) than six cycles of combination chemotherapy alone in patients with stage III or IVA endometrial carcinoma. The results indicated that chemotherapy plus radiation was not associated with longer relapse-free survival than chemotherapy alone in patients with stage III or IVA endometrial carcinoma. The Trial Outcome Index of the Functional Assessment of Cancer Therapy (FACT) for endometrial cancer (FACT-En) and the FACT/GOG-neurotoxicity (NTX) subscale were used to measure quality of life and chemotherapy-induced neurotoxic effects. Moreover, in a novel PRO methodology, two items from the FACT for colorectal cancer (FACT-C) combined with four items from the FACT-En Trial Outcome Index were used to assess gastrointestinal symptoms. After adjustment for age and baseline scores, the least-squares mean Trial Outcome Index score at 18 weeks in the chemoradiotherapy group was 5.2 points lower (97.5% CI, 2.7 to 7.8) than that in the chemotherapy-only group. The difference in this score remained significant at 70 weeks (3.4 points lower in the chemoradiotherapy group; 97.5% CI, 0.7 to 6.2), but did not exceed the six-point difference that had been preset as clinically meaningful. Patients in both groups reported symptoms of neurotoxicity in association with treatment, but the least-squares mean FACT/GOG-NTX subscale score at six weeks among patients receiving chemotherapy only was 2.0 points lower (97.5% CI, 1.4 to 2.6) than that in the chemoradiotherapy group (i.e., reflecting worse symptoms in the chemotherapy-only group). Whereas patients receiving chemoradiotherapy reported gastrointestinal symptoms at both six and 18 weeks that were significantly worse than those in the chemotherapy-only group.[3] In another endometrial cancer trial, GOG-209, PRO assessment contributed to our understanding of the limitations of the paclitaxel-doxorubicin-cisplatin (TAP) regimen, revealing that carboplatin plus paclitaxel (TC) is a noninferior alternative to TAP. Small differences in quality of life favored TC. This contributed to the recognition that with demonstrated noninferiority to TAP, TC is the global first-line standard for advanced endometrial cancer.[4] In a pivotal cervical cancer phase III clinical trial, GOG-240, the effectiveness of bevacizumab and non-platinum combination chemotherapy in patients with recurrent, persistent or metastatic cervical cancer was evaluated. The addition of bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer was associated with an improvement of 3.7 months in median overall survival.[5] Quality of life and pain assessments indicated that the addition of bevacizumab did not adversely affect quality of life, with a non-significant trend for patients receiving bevacizumab to report fewer neurotoxic symptoms, with a severity of neurotoxic symptoms similar in the two groups.[6] Further study findings represent proof-of-concept of the efficacy and tolerability of antiangiogenesis therapy in advanced cervical cancer.[7] In an additional ancillary study describing patient-reported outcomes and toxicities at time of treatment discontinuation secondary to progression or toxicities in this cervical cancer patient population, those who discontinued chemotherapy with bevacizumab for toxicity experienced longer post-protocol survival but significantly greater decline in quality of life than those with progression. This QOL decline was due to worsening physical and functional well-being, while those who discontinued treatment due to toxicities had worse neurotoxicity and pain.[8] Use of PROs in the setting of advanced gynecologic cancers have promising implications for future trials which could include supportive care interventions that might optimize function and well-being.

Quality of Life and PROs in Symptom Assessment

QOL and other PRO measurements in cancer prevention and control trials have been fundamental in several significant studies. For example, a large national trial (GOG-244) was undertaken to determine the impact of lower extremity lymphedema on QOL, psychological adjustment, physical disability and function in newly diagnosed patients undergoing surgery for endometrial, cervical or vulvar cancer. In this study a novel measure was developed to explore whether patient-reported lymphedema-related symptoms, as measured by the Gynecologic Cancer Lymphedema Questionnaire (GCLQ), are associated with a patient-reported diagnosis of lymphedema of the lower extremity (LLE) and limb volume change (LVC) in patients who have undergone radical surgery, including lymphadenectomy. The 20-item GCLQ measures seven symptom clusters-aching, heaviness, infection-related, numbness, physical functioning, general swelling, and limb swelling. LLE was defined as a patient self-reported LLE diagnosis on the GCLQ. LVC was measured by

volume calculations based on circumferential measurements. Of 987 eligible patients, 894 were evaluable (endometrial, 719; cervical, 136; vulvar, 39). Of these, 14% reported an LLE diagnosis (endometrial, 11%; cervical, 18%; vulvar, 38%). There were significantly more patients diagnosed versus not diagnosed with LLE reported ≥4-point increase from baseline on the GCLQ total score ($p < 0.001$). Changes from baseline were significantly larger on all GCLQ symptom cluster scores in patients with LLE compared to those without LLE. An LVC increment of >10% was significantly associated with reported general swelling ($p < 0.001$), heaviness ($p = 0.005$), infection-related symptoms ($p = 0.002$), and physical function ($p = 0.006$). Results from this study add significantly to the PRO measurement science literature eminating from the GOG, noting that patient-reported symptoms, as measured by the GCLQ, discerned those with and without a patient-reported LLE diagnosis and demonstrated predictive value. These results suggest that the GCLQ combined with LVC may enhance our ability to identify LLE.[9] A related study examined the impact of LLE on quality of life, daily function, and body image. In this trial, among 768 evaluable patients, those with a GCLQ score change ≥4 from baseline had significantly worse QOL ($p < 0.001$), body image ($p < 0.001$), sexual and vaginal function ($p < 0.001$), limb function ($p < 0.001$), and cancer distress ($p < 0.001$).[10] There were no significant differences in sexual activity rates between those with and without LLE symptoms. Results from these studies demonstrate the value of the GCLQ tool together with other PROs in understanding the impact of lymphedema on the gynecologic cancer patient population, underscoring the need for clinical prevention and improved treatment measures.

QOL investigators advised on patient-reported measures needed to determine the factors associated with deciding between risk-reducing salpingo-oophorectomy (RRSO) and ovarian cancer screening (OCS) among high-risk women enrolled in GOG-0199. This prospective cohort study assessed women at increased ovarian cancer risk who chose either RRSO or OCS as their risk management intervention. Of the 2,287 women who enrolled, 904 (40%) chose RRSO and 1383 (60%) chose OCS. Compared with participants choosing OCS, participants choosing RRSO were older ($p<0.0001$), more likely to carry deleterious BRCA1/2 mutations ($p<0.0001$), perceive RRSO as effective, be more concerned about surgical harms and OCS limitations, and report higher perceived OC risk and OC-related worry. OCS participants were more likely to perceive screening as effective, be more concerned about menopausal symptoms, infertility, and loss of femininity, and report better overall quality-of-life. Twenty-four percent of participants believed they would definitely develop OC, and half estimated their lifetime OC risk as >50%, both higher than objective risk estimates. Cancer worry, BRCA1/2 mutation status, and perceived intervention-related risks and benefits were associated with choosing between RRSO and OCS.[11] The authors also indicated that at baseline, participants selecting RRSO reported lower health-related QOL (HRQOL), greater ovarian cancer-related stress, greater anxiety, and more depressive symptomatology, which improved during follow-up, especially for ovarian cancer-related stress. Screening was not found to adversely impact HRQOL. Hormone-related menopausal symptoms worsened and sexual functioning declined during follow-up in both cohorts, but more so among participants who underwent RRSO.[12]

QOL and PROs served as primary endpoints in GOG-267, which evaluated quality of life, symptoms and care needs in patients with persistent or recurrent platinum-resistant ovarian cancer, in which eligible women (N=102) included those with persistent or recurrent platinum-resistant ovarian cancer with an estimated life expectancy of at least six months. The Needs at the End-of-Life Screening Tool (NEST), FACIT-Fatigue (FACIT-F), NCCN-FACT Ovarian Symptom Index (NFOSI-18), Disease Related Symptoms (DRS), Treatment Side Effects (TSE), and Function/Well Being (F/WB) were collected at study entry, three, and six months. At study entry, the most common disease-related symptoms were fatigue (92%), worry (89%), and trouble sleeping (76%); 73% reported being "bothered by treatment side effects," which included nausea (41%) and hair loss (51%) neither of which changed over time. The most common NEST unmet needs were in the symptom dimension, where symptoms were associated with DRS ($p = 0.04$), TSE ($p = 0.03$), and FACIT-F ($p = 0.04$). Results indicate that in patients nearing the end of life, there are significant associations between disease and treatment related symptoms and unmet patient needs, which do not improve substantially over time.[13] Additional analyses also indicated that use of the DRS-Physical of the NFOSI-18 was responsive to clinical change and has potential as an indicator of changing health status with ovarian cancer disease progression, distinct from treatment side effects.[14]

Quality of Life and PROs as Outcome Prognosticators

The GOG has historically contributed substantially to the growing body of literature indicating that quality of life is prognostic for several clinical outcomes.[15-18] The GOG-273 study prospectively tested the association of baseline Instrumental Activities of Daily Living (IADL) scores with ability to complete four cycles of first line chemotherapy without dose reductions or > seven days delay in elderly

ovarian cancer patients. Results indicated that patients with a higher baseline IADL score (more independent) were more likely to complete four cycles of chemotherapy and less likely to experience grade three or higher toxicity.[19] In a recent grant supported by the US Department of Defense, investigators examined the prognostic relationships between quality of life (QOL) and adverse events in long-term (8+ years) ovarian cancer survival. Results indicated that QOL differed statistically significantly between short-term (N = 1115) and long-term survivors (N = 260) ($p < .001$). Both baseline and longitudinal QOL change scores distinguished long versus short-term survivors and are considered robust prognosticators for long term survival.[20] Results from this and the studies referenced above have future trial design and supportive care implications, providing meaningful prognostic value in the advanced gynecologic cancer population.

Conclusion

The current PCOR committee of NRG Oncology reviews all phase III concepts for consideration of QOL inclusion, and advises the Cancer Prevention and Control (CPC) committee with respect to PROs. Similarly, the GOG-P trials have also incorporated robust QOL and PRO measures. These are often included to better understand treatment effects in terms of efficacy and toxicity, which provides regulatory authorities with an enhanced context for approval decisions. Taken together, QOL and other PROs continue to be incorporated as secondary endpoints into the majority of gynecologic cancer phase III clinical trials, as they capture meaningful disease and side effect burden from the patient's perspective, thus contextualizing the patient experience for both treatment and disease. QOL results contribute to overall trial interpretation, which ultimately aids in treatment decision-making. In addition, QOL and other PRO measures have been seminal to many of the prominent CPC trials. These trials have benefitted from collaborations between behavioral, nurse and physician scientists in order to introduce measures and assessment intervals which provide the greatest precision with the least burden. The measurement science that guides these decisions continues to be innovative. Building upon the early success of GOG in validating a now widely used measure for neurotoxicity (i.e., FACT-GOG/NTX), novel advancements in measurement science include refining a patient-reported lymphedema symptom questionnaire (e.g., GCLQ through the CPC committee), as well as a brief, validated ovarian cancer disease-related symptoms measure (i.e., DRS-P) for consideration in future advanced ovarian cancer trials, and a hybrid measure for potential chemoradiation-induced GI symptoms. Future directions include continued advances in QOL measurement science, continued collaboration with the disease site committees in the promising era of targeted therapies and PARP inhibitors, and consultation with scientists measuring symptoms or QOL in response to an intervention.

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