



¹Gynecology with Center of Oncological Surgery, Charite Universitätsmedizin Berlin, Berlin, Germany

²Division of Cancer Sciences, The University of Manchester, Manchester, UK

Correspondence to

Dr Robert Armbrust, Dept. of Gynecology, Charite University Hospital Berlin, Berlin, 13353, Germany; robert.armbrust@charite.de

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Health-related quality of life metrics as endpoints in surgical trials: hype or hope?

Robert Armbrust ¹, Jennifer Davies-Oliveira ², Jalid Sehouli ¹

ABSTRACT

The management of gynecological cancer has evolved considerably over the past decades in almost every field of treatment. Surgery plays a major role in the treatment algorithm. However, these invasive interventions can have profound implications for the quality of life (QoL) of affected individuals. The routine implementation of QoL measurements in clinical trials has become common, reflecting a new research ‘standard’, despite the fact that all available QoL instruments were not designed nor validated prospectively for surgical trials. This review seeks to address whether patient reported outcomes and QoL measurements rightfully take center stage in current surgical trials, leading to direct implementation for the benefit of patient care, or are they simply more of a researcher’s hope. We will also provide an ‘action plan’ to better implement QoL measurements in future surgical trials.

INTRODUCTION

Gynecological cancers, encompassing malignancies of the vulva, vagina, cervix, uterus, and ovaries, present a significant worldwide health challenge. The management of gynecological cancer has evolved considerably, with surgical interventions playing a pivotal role in the diagnostic, curative, and palliative phases of treatment. In advanced ovarian cancer, for example, surgery is a cornerstone of treatment, offering disease control potential and survival benefits.^{1,2} However, these invasive interventions can have profound implications for the quality of life (QoL) of affected individuals.^{3–5}

Surgical procedures for gynecological cancer often entail the removal of reproductive organs, lymph nodes, and, potentially, parts of the gastrointestinal and urological tracts.^{6,7} While these interventions are important for disease management, they can lead to various negative physical and psychosocial impacts. Studies have consistently reported immediate post-operative effects, including pain, fatigue, and decreased mobility, which can diminish overall QoL.⁸ Additionally, long-term consequences, such as altered body image, sexual dysfunction, and infertility, demonstrate the enduring impact of these interventions.⁹

However, recent research also shows that even extensive multivisceral surgery does not appear to result in poorer or inferior QoL in ovarian cancer

patients.³ Evidence demonstrates consistently that increasing surgical radicality in advanced ovarian cancer fails to translate into a negative long-term impairment of patients’ QoL compared with less radical surgery. In fact, findings suggest significantly higher global QoL scores, compared with baseline, within the first post-operative year despite patients’ exposure to radical multivisceral resection techniques.^{10,11} The routine implementation of QoL measurements in clinical trials is much more common, reflecting a new research ‘standard’, despite the fact that all available QoL instruments were not designed nor validated prospectively for surgical trials. Furthermore, the focus in these trials was mainly on morbidity, mortality, and overall survival, not QoL.

This review seeks to address whether patient reported outcomes and QoL measurements rightfully take center stage in current surgical trials, leading to direct implementation for the benefit of patient care, or are they simply more of a researcher’s hope. We will also provide a 10 point ‘action plan’ to better implement QoL measurements in future surgical trials.

Current Controversies in Surgical Approaches and QoL Measurements

Even though the primary treatment of ovarian cancer is complex, the novel findings of revolutionary research, especially in the past decade, has led us to a completely new era of investigation and management. Surgical management remains one the most important prognostic factors directly associated with survival outcomes. However, the optimal timing of surgery is heavily debated and whether a less radical surgical approach facilitated with neoadjuvant chemotherapy is less harmful representing a more ‘elegant’ management strategy. One such argument for this approach is the effect of ‘radical’ primary surgical techniques, including increasing the rate of multivisceral resections. In the international SOCQER-2 trial, the primary outcome assessed global score differences in the European Organization for Research and Treatment of Cancer (EORTC) core quality-of-life questionnaire (QLQ-C30) in those undergoing primary surgery for ovarian cancer. Overall 293 patients were recruited. The conclusions of this trial were clear: complex extensive and radical surgery did not adversely impair QoL. Moreover, further evaluation at



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Review

12 months post-treatment showed an improvement in global QoL after surgery.³

We wait with anticipation for the results of the TRUST trial which seeks to further delineate the QoL impact of primary debulking surgery versus interval debulking surgery, in the era of adjunctive poly (ADP-ribose) polymerase (PARP) inhibitors, prehabilitation, and enhanced recovery after surgery (ERAS), within strict surgical assurance criteria.¹²⁻¹³ The validation and implementation of prehabilitation and ERAS concepts has shown the importance of classifying patients as non-frail, pre-frail or frail prior to any treatment to enable adoption of the best management strategies, which will undoubtedly affect prospective QoL. The term ‘frailty’ describes the individual patient condition for several health aspects which contribute to morbidity. There is already evidence for the importance of prehabilitation programs as well as the implementation of ERAS guidelines, which if implemented together appear to have a positive synergistic effect on effect on post-operative morbidity.

The LION trial, a large randomized controlled trial conducted in high-volume and high-quality European centers, showed in a sexual health subgroup analysis the importance of QoL effects and surgical complications. The results showed that a systematic lymph node dissection in patients without bulky lymph nodes does not improve overall survival and progression-free survival but is associated with a significantly higher morbidity and negative QoL impact. The data showed that patients who underwent full lymph node dissection reported significantly higher rates of pain during sexual intercourse.¹⁴

The LACC trial, comparing minimally invasive and open surgical routes for radical hysterectomy in cervical cancer, revealed that the minimally invasive route was associated with worse disease-free survival and overall survival rates compared with the open route. Furthermore, the rate of local recurrence and distant metastases was also significantly higher in the minimally invasive surgery group. Secondary outcomes revealed that there were no significant differences in QoL measurements and complications between the two surgical approaches.¹⁵ By contrast the recently reported SHAPE trial, investigating the role of a simple versus a radical hysterectomy for the management of early stage cervical cancer, showed, as a secondary endpoint, that a radical procedure was associated with a significantly higher incidence of post-operative urinary incontinence and retention.¹⁶ We await validation of these findings in the final results with anticipation.

The implementation of QoL parameters is crucial in surgical trials for gynecological malignancies, as findings from these can inform important treatment decisions and therefore have an impact on long-term health. In addition, it has been shown that patients also value health-related QoL (HRQoL) information and can interpret HRQoL findings accurately. Nonetheless, there is room for improvement as some common QoL issues related to surgical management of gynecological malignancies are rarely addressed, despite a growing evidence base and the development of validated prediction tools. For example, Yost et al have developed and successfully validated a questionnaire for the early detection of peripheral lymphedema, a common risk following a full lymphadenectomy.¹⁷ However, our own findings have suggested the consistent under-reporting of lymphedema,¹⁸ highlighting that QoL parameters may remain unexplored in clinical practice despite evidence highlighting the importance of this in the management of gynecological cancers.

Controversies About Current QoL Parameters, Possible Improvements and Their Prognostic Role

Several older studies have shown that self-reported health or HRQoL variables have independent prognostic power for survival.¹⁹ Most important predictors were global QoL, functioning scales, and symptoms such as fatigue, appetite loss, and pain, despite adjusting for sociodemographic and clinical factors.²⁰ The EORTC QLQ-C30 summary score, physical functioning, and global QoL were strong predictors for mortality in a large sample of nearly 7000 patients with 12 different cancer types.²¹ However, there are conflicting data in ovarian cancer patients. Two studies revealed that baseline scores on the Functional Assessment of Cancer Therapy-General (FACT-G) and the Treatment Outcome Index of the FACT-Ovarian are significant predictors of mortality.²²⁻²⁴ In addition, another two trials demonstrated that all functioning scales of the EORTC QLQ-C30 except global QoL were univariably significantly related to mortality.²⁵⁻²⁶ In contrast, Gupta et al could not show any significant association of functioning scales at baseline with mortality in ovarian cancer patients.²⁷

These differences may be attributed to cohort heterogeneity of primary and recurrent ovarian cancer groups as well as early and advanced stage disease. Another argument could be that these QoL measurement instruments were not specifically designed for gynecological cancer, and were developed many years ago and did not anticipate treatment advances. Another challenge, when undertaking multivariable analyses, is the inconsistency that may be caused by the intercorrelation of HRQoL variables and clinical variables, making it difficult to identify the most important QoL predictors.²¹ Timing of QoL measurement is also important as highlighted by pre-operative QoL potentially having a direct impact on post-operative complications.²⁸ This information is suggestive of a prognostic role for pre-surgery QoL parameters, highlighting the importance of this metric in management decision making. Additionally, in clinical oncology trials it was shown that 69.8% of studies assessed QoL during treatment, but this dropped to 3.4% during long-term follow-up until death.²⁹⁻³⁰ This highlights the need to consider long-term QoL measurement in trials as many treatments can have long-term effects and if these are not measured then the true impact of an intervention cannot be fully appreciated.

While the inclusion of HRQoL parameters as endpoints in surgical trials is important, there is some concern regarding the implementation and interpretation of these. Indeed, Calvert et al in their *Lancet* commentary state ‘trials that incorporate HRQoL as an outcome should therefore be designed, analyzed and reported well’. Bridoux and colleagues found methodological limitations in 24 published randomized controlled trials (RCTs) concerning gastrointestinal surgery reporting on HRQoL, with up to 37% giving no information on missing data, 46% failing to report information on the administration of the HRQoL measure, and only 1/5 stating the rationale for selecting a specific HRQoL measure.³¹ In addition, Brundage et al³² showed data similarly lacking in 794 RCTs across a range of medical conditions reporting on HRQoL, concluding that trials reporting variances negatively impact on the use of HRQoL data for application in clinical practice. To maximize the utility of HRQoL outcomes it is important to use reliable and valid HRQoL measures that are appropriate for the population of interest, co-created and agreed by clinicians, researchers, and patients.³³ In addition, assessment timing must be relevant to clinical interpretation of results, with missing data

minimized and prespecified statistical analyses used to avoid selective reporting of results.³⁰ The CONSORT-PRO (Consolidated Standards of Reporting Trials) is an extended statement to improve the reporting of patient reported outcomes (PROs) in RCTs and is likely to help standardize HRQoL reporting. The statement encourages the reporting of PROs in the abstract, a description of the hypothesis of the PROs, evidence of the PRO instrument's validity and reliability, a statement of the statistical approaches for dealing with missing data, and the reporting of PRO-specific limitations and generalizability to other populations and clinical practice to be discussed.³⁴

However, despite the possible limitations of HRQoL measurements, global HRQoL and relatively 'simple' clinical parameters can be prognostically relevant, even in complex treatment situations such as recurrent, platinum-resistant ovarian cancer. The newly developed North-Eastern German Society of Gynecological Oncology-Working Group Gynecological Oncology (NOGGO-AGO) QoL prognosis score discriminates well between recurrent ovarian cancer patients under low, medium, and high risk of short-term mortality. It could help to identify the group at high risk of short-term mortality and could be used for randomization in clinical trials to support decision making for palliative chemotherapy. As a direct consequence, this score will be prospectively implemented in all NOGGO prospective trials.²¹

Action plan for QoL implementation in surgical trials:

- ▶ QoL measurements should be routinely implemented in surgical and non-surgical clinical trials
- ▶ Trial design should be specific to the QoL question being addressed, for example, lymphedema or morbidity or global QoL
- ▶ Clear definition of the endpoints including progression-free survival and its possible effects on QoL and morbidity
- ▶ Only use validated questionnaires
- ▶ QoL should be measured at different timepoints in the cancer journey including pre-operative, post-operative in the short- and long-term—this enables personalized evaluation and management of QoL issues
- ▶ Statistical power estimation regarding QoL should be emphasized, with power calculations not to be based on progression-free survival/overall survival alone
- ▶ High response rates regarding QoL measurements (minimum above 50%)
- ▶ Ensure to include the CONSORT PRO checklist items.

CONCLUSION

Surgery undoubtedly plays a vital role in gynecological disease management, but it carries implications for the QoL of affected individuals. Understanding the multifaceted effects of surgery on physical, emotional, social, and sexual well-being is essential. Advancements in peri-operative care and surgical techniques, coupled with comprehensive multidisciplinary support, hold promise in improving the overall QoL of gynecological cancer survivors. Further research and tailored interventions are needed to address the unique challenges faced by this patient population. Multidisciplinary care, including physical, psychological, sexual, and social support, has become increasingly recognized as integral to addressing the holistic needs of gynecological cancer patients. These interventions aim to mitigate the negative impact of surgical interventions on QoL.

Twitter Jennifer Davies-Oliveira @JenOG

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ORCID iDs

Robert Armbrust <http://orcid.org/0000-0002-8606-6523>

Jennifer Davies-Oliveira <http://orcid.org/0000-0002-0193-0053>

Jalid Sehouli <http://orcid.org/0000-0002-5963-6623>

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Review

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