# Quality of Life in Women with Ovarian Cancer

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## Introduction

Ovarian cancer and its treatment can have a profound impact on health-related quality of life (HRQL) in both the short and long term. Understanding these impacts is essential for evaluating the effects of treatment from the patient's perspective, as well as for managing the care of individual patients. HRQL can be assessed for research purposes or within clinical practice, and if availed of fully, can form a key component of patient-centred care. HRQL data from clinical research can help to guide improvements in clinical practice as well as to advise patients about the possible impact of treatment, thereby assisting patients to make informed decisions about treatment. The assessment of HRQL within clinical practice can aid communication between the treating clinician and the patient about the issues that are affecting the patient's quality of life. This, in turn, can help the clinician to be more adept at both identifying and managing patient problems. In this chapter, we introduce key terminology and discuss how ovarian cancer and its various treatments affect patients' HRQL in terms of the disease symptoms, treatment side effects and broader impacts on physical and psychological functioning.

## Terminology and Definitions: HRQL and PROs

A definition of *health-related quality of life* (HRQL) that is useful for clinical research and health services research is:

> *Health-related quality of life (HRQL) is a multidimensional construct encompassing perceptions of both positive and negative aspects of dimensions, such as physical, emotional, social, and cognitive functions, as well as the negative aspects of somatic discomfort and other symptoms produced by a disease or its treatment* [1].

A fundamental component of this definition is that HRQL is a *multidimensional* concept that includes both core domains and symptoms that differ as a function of the disease type and treatment. It is also a *subjective* phenomenon, meaning that the patient's appraisal of their functioning

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and symptoms is preferable to that of a proxy such as a clinician or family member [2].

Apart from patients' symptoms and functioning, many other aspects of a patient's experience of disease and treatment can have an impact on their HRQL. For example, patients' satisfaction with care, their unmet needs for information or support services, and their psychological adjustment to illness can also negatively affect their HRQL.

A related umbrella term is *patient-reported outcome (PRO)*. This term emerged to solve the difficulty of finding a universal and all-encompassing definition of HRQL and its related concepts. A PRO is defined as:

> *A patient-reported outcome (PRO) is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else* [3].

As an umbrella term "PRO" does not shed light on what is measured in any specific case, but emphasises that the patient provides the assessment. PROs can be symptoms (e.g. pain, anxiety, nausea, fatigue), aspects of functioning (e.g. physical, emotional, sexual, social), or multidimensional constructs (e.g. HRQL). For the purpose of this chapter, the PRO of interest is HRQL.

## How Ovarian Cancer Affects HRQL

High-grade serous ovarian cancer is the most common subtype of ovarian cancer and the most lethal of all gynaecological cancers. Although women with early-stage disease (stage 1A or 1B) have an excellent prognosis, the majority (up to 70%) of women are diagnosed at an advanced stage and less than half of these women will survive beyond 5 years [4]. Unfortunately, following initial treatment, the majority of women will develop a recurrence and with each recurrence the chance of cure diminishes. Throughout all phases of the disease and treatment trajectory, ovarian cancer and its treatments can have wide-ranging impacts on HRQL. Importantly, the value women with ovarian cancer place on different types of treatment outcomes is likely to vary, and the extent to which women will be willing to compromise their HRQL for possible survival gains will differ, particularly as the disease progresses [5].

Although ovarian cancer has often been characterised as a "silent disease" because many women only present with signs and symptoms at an advanced stage of the disease, there is increasing evidence that women with ovarian cancer do have recognisable symptoms before diagnosis [6]. One of the most commonly reported symptoms is abdominal pain, but many women also report abdominal bloating, feeling full quickly, difficulty eating and in some cases urinary symptoms [6]. Some women may also experience abnormal vaginal discharge and postmenopausal bleeding before diagnosis [7].

Receiving a diagnosis of ovarian cancer is often a traumatic shock to patients and causes considerable distress, especially because many women often misattribute their symptoms to other less serious conditions [8]. Many patients experience additional distress after treatment as surgery and chemotherapy can cause burdensome side effects including a number of physical symptoms and physical changes (see section on Treatment-Specific HRQL: Symptoms and Side Effects of Treatment). Some side effects and changes may persist long after treatment ends, such as psychosexual problems. These physical and psychological disturbances can adversely affect HRQL and impact on women's ability to perform their usual daily tasks and activities.

Surgery to remove or reduce the extent of the cancer may be preceded and/or followed by adjuvant chemotherapy. For a minority of women with ovarian cancer, treatment can be curative or result in long-term survival, but for the majority treatment is palliative and intended to slow down or reverse cancer growth and reduce the symptoms caused by the disease. Although palliative treatment may extend survival, it may also induce side effects. PROs are particularly important within a palliative context, and in these contexts may be suitable primary endpoints [9]. This is particularly true for clinical trials of patients with platinum-resistant/refractory ovarian cancer,

where the impact of treatment on HRQL and symptom benefit should ideally be used as co-primary endpoints with traditional endpoints such as progression-free survival and overall survival [10].

## Proximal Versus Distal Effects on HRQL

Figure 13.1 provides a graphical depiction of how the symptoms of ovarian cancer and the side effects of its treatments may affect a woman's functioning and HRQL. Proximal effects occur directly as a consequence of the disease and/or treatment [11], such as the symptoms of ovarian cancer (e.g. abdominal pain and bloating) and the side effects of treatment (e.g. nausea, skin rash). In turn, these symptoms and side effects may affect the woman's functioning and overall HRQL (i.e. cause distal effects). A diagnosis of ovarian cancer, its treatment and recurrence can impact psychological well-being directly (i.e. proximally) or indirectly via disease and/or treatment-related symptoms and loss of functional ability.

It is important to consider the proximal and distal effects of disease and treatment when deciding which PRO instrument to use in ovarian cancer research or clinical practice. The more proximal an outcome is to the disease or treatment, the more likely it is to detect treatment effects [11]. In contrast, the more distal an outcome is, the more likely it is to be affected by other factors that are external to the treatment [11]. For this reason, a proximal outcome such as abdominal symptoms may be an appropriate key PRO for an ovarian cancer clinical trial, and a suitable questionnaire must be found. *Good candidates are described in* section "Choosing a PRO Instrument", *along with the general principles guiding instrument selection*. The AURELIA trial illustrates the use of patient-reported abdominal symptoms as the key PRO in a Phase III trial for platinum-resistant ovarian cancer, along with more distal aspects of HRQL as secondary PROs [12].

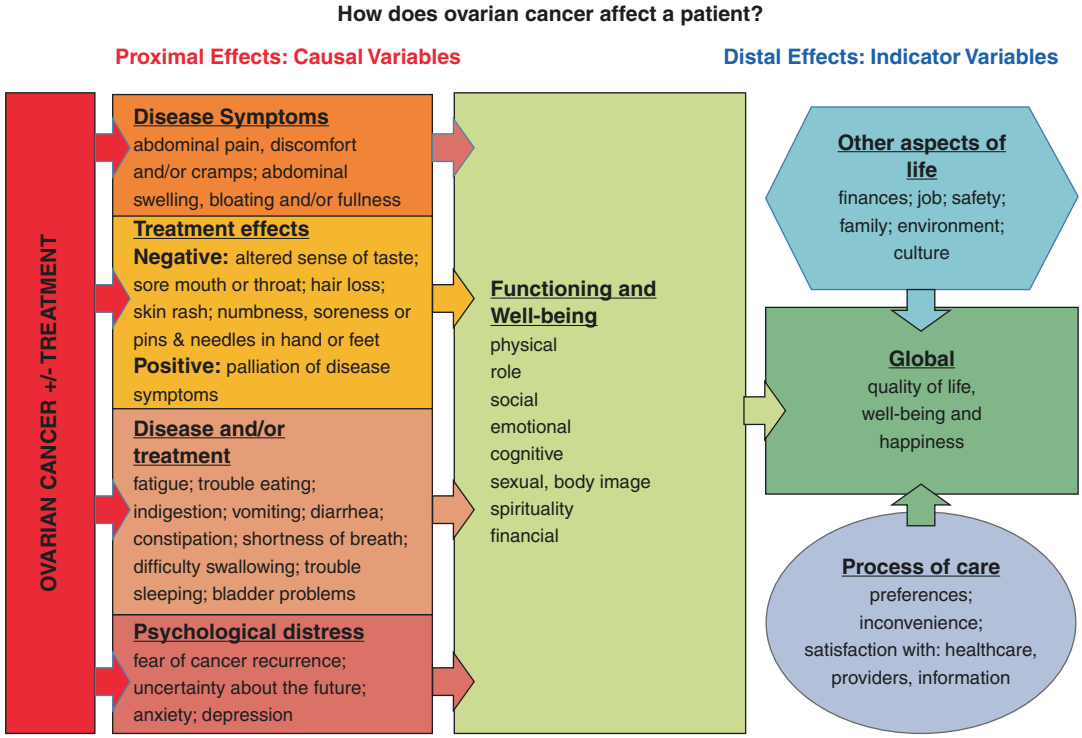


**Fig. 13.1** Ovarian cancer effects on HRQL

## Treatment-Specific HRQL: Symptoms and Side Effects of Treatment

The main treatment modality for most women with primary ovarian cancer is cytoreductive surgery and chemotherapy. The goal of first-line treatment is to eradicate or reduce the volume of disease, without severely compromising HRQL [13]. Unfortunately, despite high remission rates following first-line treatment, 80% or more will develop recurrent disease [14]. Women with recurrent disease may undergo repeated cycles of chemotherapy so careful consideration of the impact of treatment on HRQL is needed to ensure that the benefits of treatment outweigh the toxicities. Patient reports of the side effects of treatment and their impact on HRQL are paramount for understanding the risks versus benefits of treatment from the patient's perspective.

### Surgery

The mainstay of treatment for all stages of ovarian cancer is cytoreductive surgery. This involves comprehensive surgical staging as well as a total abdominal hysterectomy and bilateral salpingo-oophorectomy to remove the uterus and cervix along with the fallopian tubes and ovaries. Depending on the extent of disease, surgery may also involve omentectomy, lymph node dissection and bowel, liver or spleen resection [15]. The extent of successful tumour cytoreduction following surgery is considered to be the most important prognostic factor for long-term survival [15]. For premenopausal women, cytoreductive surgery renders women infertile (*the impact of loss of fertility and early onset menopause on young women is described in* section "Psychological Impact"). Only very selected young women with early-stage disease and specific histological subtypes may be eligible for fertility-sparing surgery [16].

Although a number of studies have examined the impact of chemotherapy on the HRQL of women with ovarian cancer, relatively few studies have examined the direct impact of cytoreductive surgery alone (and not in combination with chemotherapy) on PROs. One study, which assessed PROs in women with suspected primary ovarian cancer pre- and 1 month post-surgery, indicated that the most common post-operative complications reported after surgery were wound infections, fever and sepsis, followed by ileus, nausea and vomiting [17]. After surgery (i.e. prior to chemotherapy) patients report severely impaired HRQL as evidenced by high levels of fatigue, anxiety and depression and lower scores on all functioning domains [18].

A longitudinal cohort study of women with early- and late-stage ovarian cancer that underwent standard or extensive cytoreductive surgery found that global HRQL (that is, based on questions that asked directly about "quality of life" rather than specific aspects of it) deteriorated from baseline to 3 months after surgery in both the standard and extensive surgery group [19]. Notably, the women that had extensive surgery reported greater deterioration in global HRQL, functioning and symptom scores than women who had standard surgery [19].

In circumstances where optimal cytoreduction (i.e. zero residual disease) is not considered achievable because of a very large bulk of disease or because patients are unfit for surgery, neoadjuvant chemotherapy (NACT) may be administered first to reduce tumour volume followed by interval debulking surgery. One trial (EORTC GCG 55971) compared the impact of primary debulking surgery (PDS) versus interval debulking surgery (IDS) after NACT on HRQL and found that survival and HRQL were similar in both treatment arms [20]. All patients showed a clinically relevant improvement (>10 points) in global HRQL, role functioning, and social functioning during and after treatment independent of the treatment arm. Another study compared the symptom burden and functional recovery of women undergoing PDS or IDS following NACT and found that there were no significant differences in the symptoms reported by women both in the immediate in-hospital period and in the extended post-hospital discharge period [21]. However, irrespective of the timing of the surgery in relation to chemotherapy, women that under-

went intermediate or high complexity surgery reported more nausea, fatigue and greater interference of symptoms with their mood and daily activities [21].

## Chemotherapy

Chemotherapy before or after surgery is standard treatment for all women with ovarian cancer except for a small minority with selected subtypes of early-stage disease and favourable histology, for whom adjuvant chemotherapy is not recommended [22]. The standard chemotherapy is a platinum-taxane combination regimen [22]. Bevacizumab may also be added to combination chemotherapy in women with advanced disease who have significant residual disease at the completion of surgery.

Women with ovarian cancer may experience a number of treatment-related symptoms during chemotherapy. Common physical symptoms include hair loss, altered sense of taste, sore mouth or throat, skin rash, fatigue, nausea or difficulty swallowing [23]. In a qualitative study, women who had received first-line chemotherapy described hair loss as the most distressing physical symptom of the ovarian cancer experience because it led to a loss of sense of self and altered body image, and served as a reminder of their illness and potential for an early death [24]. Sexual dysfunction and intimacy issues are also prevalent during chemotherapy and there is evidence that patients report significantly worse menopause-related symptoms and body image during first-line chemotherapy compared to women who have already received multiple lines of chemotherapy [25].

Long-term side effects of chemotherapy include pain and fatigue, which can persist years after treatment has ended [26]. Peripheral neuropathy is a debilitating long-term side effect which can persist in 50% of women with ovarian cancer who receive chemotherapy even up to 12 years after the end of treatment [27]. The platinum and taxane-based chemotherapies used for ovarian cancer damage predominantly sensory nerves, manifesting as tingling or numbness in the hands and/or feet [28, 29]. Consequent fine-motor dysfunction causes difficulties in daily tasks such as typing, holding objects securely, doing up buttons and putting on braziers and necklaces. Lower limb problems with balance and walking lead to slips, trips and falls and reduced ability to exercise [30].

Apart from physical symptoms, women receiving chemotherapy may also experience considerable psychological distress. A study among women with recurrent ovarian cancer found that all women reported high levels of anxiety and depression throughout the course of chemotherapy. However, levels of anxiety significantly decreased during active chemotherapy whereas levels of depression did not. Notably, both anxiety and depression were associated with poor HRQL on all functioning and symptom domains, both at baseline and during active chemotherapy [31].

Importantly, chemotherapy can also affect the HRQL of patients positively, by alleviating symptoms and slowing, halting or reversing deteriorations in functioning. Among women with recurrent disease and poor prognosis, chemotherapy can help to manage symptoms by reducing abdominal swelling, bloating, and/or fullness; abdominal pain, discomfort, and/or cramps; and anxiety [23]. Furthermore, in a study by Doyle et al., women with advanced ovarian cancer receiving second-line chemotherapy reported improved emotional functioning even though clinical data indicated that only a minority of patients benefited from treatment in terms of tumour shrinkage [31]. This raises the issue of whether the treatment itself or the hope provided by having the treatment led to these favourable outcomes. It is especially important for women with recurrent disease receiving palliative chemotherapy that these positive effects are carefully balanced against the possible adverse effects to determine the potential value of the treatment for individual patients.

Chemotherapy is usually administered as an intravenous (IV) infusion; however, in selected patients with stage III ovarian cancer whose tumour was optimally debulked, intraperitoneal (IP) chemotherapy may be given by infusion of

the chemotherapy drug directly into the peritoneal cavity. A meta-analysis of nine clinical trials which examined whether adding a component of the chemotherapy regime into the peritoneal cavity affects survival and HRQL revealed that IP chemotherapy prolonged both overall and progression-free survival [32]. However, IP chemotherapy was associated with greater toxicity in terms of pain, fever, gastrointestinal problems and infection than the IV route [32]. Thus, the decision to use IP chemotherapy should be made on a case-by-case basis, weighing up the potential for survival gains and individual tolerance of toxicities.

After chemotherapy for ovarian cancer, women attend regular follow-up appointments for disease surveillance. At follow-up, patients typically receive a clinical examination and a blood test for the ovarian cancer tumour marker CA-125 to monitor treatment response and detect any recurrence. Findings from the MRC OV05/EORTC 55955 trial indicated that asymptomatic patients who attained a complete response after first-line treatment, and received early second-line treatment on the basis of elevated CA-125 levels alone, had no survival benefit and poorer HRQL compared to women who received delayed second-line treatment after recurrence was detected through clinical examination [33]. Thus, findings from this trial indicate that among women who had complete response to first-line treatment, further treatment is not indicated by rising CA-125 levels alone, and can be safely delayed until symptoms or signs of tumour recurrence develop [20]. To this end, a decision aid has been developed to assist asymptomatic women with rising CA-125 levels to make informed decisions about when to initiate second-line treatment [34].

## Targeted Therapy

Bevacizumab is a targeted therapy that belongs to a class of drugs called angiogenesis inhibitors. Bevacizumab attaches to a protein called vascular endothelial growth factor (VEGF) which inhibits cancer growth. The AURELIA trial found that adding bevacizumab to standard chemotherapy for women with recurrent platinum-resistant ovarian cancer achieved an approximate doubling of the proportion of patients who experienced a 15% improvement in patient-reported abdominal symptoms [12]. Better outcomes with bevacizumab were also achieved for global QOL and physical, role and social functioning. More recently, a review of randomised phase III trials evaluating the effectiveness of a combination of bevacizumab plus standard chemotherapy for first-line treatment of advanced ovarian cancer reported both clinical and HRQL benefits of bevacizumab. Specifically, the review concluded that bevacizumab extends progression-free, but not overall, survival and improves patient-reported abdominal symptoms in women with recurrent ovarian cancer [35].

Targeted therapy using inhibitors of the enzyme poly ADP ribose polymerase (PARP) is another type of therapy which is increasingly being used in the management of ovarian cancer. PARP inhibitors are used both as a single-agent treatment for relapsed ovarian cancer as well as for maintenance therapy after chemotherapy to prolong the duration of response or the disease-free interval following chemotherapy. For example, olaparib has been shown to be effective at prolonging progression-free survival after second-line platinum-based chemotherapy, especially among patients with a BRCA1/2 mutation [36]. Current evidence indicates that maintenance treatment with olaparib is well tolerated and has no adverse effects on HRQL among patients with recurrent ovarian cancer who responded to their most recent platinum-based therapy compared to a placebo tablet [37, 38]. Furthermore, the SOLO2 trial demonstrated that olaparib maintenance therapy resulted in clinically meaningful patient-centred benefits in terms of higher TWiST scores (defined as time without significant symptoms of toxicity) and quality-adjusted progression-free survival compared with placebo [38]. However, PARP inhibitors have been shown to result in patient-reported adverse effects such as low-grade fatigue, nausea and vomiting [38].

## Psychological Impact

Ovarian cancer and its treatment are aggressive by nature, which is often very distressing for the woman. From initial diagnosis through acute treatment to survivorship, psychological distress is significantly more common among women with ovarian cancer than healthy women [39]. Many patients report symptoms of anxiety and depression and some even report symptoms of post-traumatic stress disorder [39, 40]. In qualitative interviews, patients describe the experience of diagnosis and treatment for ovarian cancer and the potential for an early death as an existential assault that severely affects the patient and her relationships [40]. A prospective cohort study examined predictors of psychological distress among ovarian cancer patients and found that higher symptom burden, lower optimism and receiving specialist mental health treatment were all associated with depression and anxiety, whereas lower social support was only predictive of patient anxiety [40].

Due to its high rate of recurrence, women with ovarian cancer commonly report fear of cancer recurrence (FCR) [41]. A systematic review of FCR in ovarian cancer patients revealed that FCR was a significant concern for both younger and older women at both early and advanced stages of the disease [41]. Women report feeling distressed about the possibility of recurrence both during and post-treatment, and report FCR to be particularly prevalent during follow-up examinations [41]. FCR is associated with patients' anxiety about death and dying as well as uncertainty about their future. Many ovarian cancer patients report not receiving adequate support for their FCR [41].

## Loss of Fertility and Early Menopause

While the minority of women diagnosed with ovarian cancer are young, treatment can have life-changing consequences including infertility and early onset of menopause. For premenopausal women, treatment can result in infertility through the surgical removal of the reproductive organs and the administration of chemotherapy drugs that are toxic to the ovaries. Most premenopausal women will experience abrupt menopausal symptoms after cytoreductive surgery or chemotherapy [42]. These menopausal symptoms may include hot flashes, mood changes, and vaginal dryness or atrophy [43]. Apart from the physical symptoms and mood changes caused by early menopause, the loss of fertility can also have a profound psychological impact, particularly on women who had wanted to have children. For young women who are not eligible for fertility-sparing surgery, losing fertility following treatment can be very difficult to cope with and feelings of depression, grief and stress are common [44]. This emotional difficulty may be compounded by the fact that these women have to cope with the loss of fertility while also preparing for or already dealing with chemotherapy-induced toxicities. Furthermore, for some young women, infertility may be unexpected because they were unable to take in or recall all of the information they received about the side effects of treatment during the consultation with their oncologist [45], potentially exacerbating the subsequent emotional distress.

## Psychosexual/Sexual Function (Problems Preventing/Interfering with Ability to Have Sex)

Sexual function is an important aspect of women's HRQL. Unfortunately, sexual dysfunction is common after surgical cytoreduction and chemotherapy [42]. As a result, many women experience issues with sexuality and intimacy after treatment, which can adversely affect their personal relationships [42]. Ovarian cancer survivors report lower levels of sexual pleasure and higher levels of sexual discomfort than age-adjusted controls from the general population [46]. When attempting sexual intercourse, ovarian cancer survivors experience more problems with vaginal dryness, discomfort and pain compared to healthy women [47]. Ovarian cancer survivors also report significantly less interest in sex, with more than 50% reporting a lack of

sexual desire compared to only 25% of healthy controls [46]. Several factors have been identified which predict worse sexual function among ovarian cancer survivors including increasing age, poorer mental health status and having undergone premenopausal oophorectomy and chemotherapy [46].

## Supportive Care Needs of Women with Ovarian Cancer

A cross-sectional descriptive study sought to identify the supportive care needs of women with ovarian cancer of variable stages of disease and treatment who attended a comprehensive outpatient cancer centre [48]. Eight of the top ten most frequently reported unmet needs were psychosocial. These included FCR (72%) or fear of cancer spreading (70%), concerns about the worries of those closest to them (58%), uncertainty about the future (56%), feelings of sadness (50%), changes in usual routine and lifestyle (50%), worry that the success and/or failure of their treatment are beyond their control (48%), and feeling depressed or down (46%) [48]. Two unmet physical needs frequently reported were lacking energy (56%) and not being able to do the things they used to do (52%) [48]. A literature review of the social and psychological needs of ovarian cancer survivors further identified sexual activity and sexual satisfaction as frequently reported unmet needs as well as distress, anxiety and depression [49]. The review further indicated that younger ovarian cancer survivors were more likely to have greater distress and lower HRQL compared to older survivors [49]. Together, these findings highlight the need for targeted early intervention among ovarian cancer patients to address and support these unmet needs.

Individualised nurse-led supportive care interventions may help to manage patients' physical and psychological symptoms and improve the HRQL of women with ovarian cancer. In a pilot randomised controlled trial (RCT) that examined the effects of an interactive web-based symptom management intervention, which facilitated direct communication between women with recurrent ovarian cancer and a dedicated nurse, women reported decreased symptom severity and lower distress after the intervention [50]. Another study of the provision of nurse-led follow-up versus conventional medical follow-up found that ovarian cancer patients who had received individualised nurse-led follow-up reported higher satisfaction and HRQL [51]. In addition, an 8-week comprehensive care programme consisting of group education, self-help group support, home-based exercise and relaxation was found to be an effective nursing intervention for improving the HRQL of ovarian cancer survivors [52].

Exercise and lifestyle interventions may also help to promote the physical and psychological well-being of ovarian cancer patients. After a 12-week exercise intervention during chemotherapy consisting of 90 minutes of low to moderate exercise per week, participants reported significant improvements in their fatigue, mental health and HRQL [53]. Similarly, another study demonstrated that women with ovarian cancer that participated in an individualised walking intervention during chemotherapy reported improvements in physical symptoms and physical functioning following the intervention [53]. Although these studies suggest that exercise may be beneficial for women receiving chemotherapy, future RCTs are needed to confirm these preliminary findings. To address this gap, a phase III RCT (ECHO trial) is currently recruiting 500 patients in Australia to evaluate the effect of exercise during chemotherapy on the physical well-being of women receiving first-line treatment for ovarian cancer.

## Impact on Partners/Caregivers

Ovarian cancer is not only distressing and burdensome for patients, but also significantly impacts family members, who are often required to take on the role of caregiver and to provide emotional and practical support as well as physi-

cal care to the patient. Given that ovarian cancer is a disease characterised by multiple recurrences and many lines of chemotherapy, the need to provide prolonged support and care to women with ovarian cancer can put considerable strain on the women's partner or caregiver's own functioning and HRQL over time.

In a qualitative study, the spouses of women with ovarian cancer described the emotional, psychological, and social impact of living with a partner with ovarian cancer [54]. Specifically, the spouses expressed the emotional devastation of the initial diagnosis, the ovarian cancer becoming a new focus/priority, changes to the marital relationship and the burden of providing support and having to rely on other family members [54]. A longitudinal study of women with ovarian cancer and their partners provided further insights into how the ovarian cancer experience affects women and their spouses over time [55]. While the women reported consistently compromised emotional well-being across a 3-year period, their husbands only reported worse emotional well-being at year 3. Insomnia, fatigue, and worry were problematic for both members of the couple over time, with no significant differences between women and their spouses, except that the women experienced more insomnia 3 months post-treatment [55]. These findings underscore the impact ovarian cancer has on women and their partners and underline the need to assess both the patients and their partners HRQL.

Another longitudinal study examined the HRQL of caregivers of women with ovarian cancer during the last year of life [56]. Findings revealed that caregivers had significantly lower mental and physical HRQL than population norms and demonstrated that caregiver distress and unmet needs increased throughout the year [56]. The highest unmet needs in the last year of life were difficulties managing concerns about prognosis, fear of cancer spread, balancing the patients' and their own needs, the impact of caring on work, and making decisions in the context of uncertainty [56]. Optimism, social support, higher unmet needs, the physical well-being of the caregiver, time to death, but not patient HRQL, emerged as significant predictors of caregiver mental well-being and distress [56]. These findings highlight the need to provide increased support to caregivers, particularly during the end-of-life phase.

## Why Assess HRQL in Patients with Ovarian Cancer?

There is now wide-spread support from clinical trials groups, cancer institutes, drug regulatory bodies and the pharmaceutical industry for incorporating information about the possible impact of treatments on HRQL into the treatment decision-making process [3, 57–60]. This is particularly true in ovarian cancer, given the potential benefits and risks associated with treatment.

**Reasons for Assessing HRQL in Ovarian Cancer Clinical Trials and Clinical Practice [2, 9, 61–63]**

- Baseline HRQL serves as an independent prognostic factor for survival and locoregional control.
- In some cases, HRQL may be more sensitive and/or responsive to treatment effects than clinical measures of toxicity.
- HRQL data may provide clinicians useful information when communicating with patients about their expectations and assist the patient and clinician in treatment decision-making through better understanding of treatment benefits and risks during the acute and survivorship phases (e.g. impact of chronic side effects).
- Information about potential impacts on HRQL may help patients make decisions about treatments with their clinician, and make informed decisions based on what others have experienced (i.e. the possible and likely treatment effects).
- PROs can be used to help identify the patients who are most likely to benefit from psychosocial interventions.

## How is the HRQL of Patients with Ovarian Cancer Assessed?

Historically, clinicians may have informally assessed the impact of ovarian cancer and treatment on patients' HRQL by simply asking the patient. However, there would likely be large variation in whether and how a range of possible questions are asked as well as how patients respond. A more standardised approach enables more reliable quantification, statistical analysis and comparison. This is achieved by administering validated questionnaires which include unambiguous questions about issues that are relevant to the patient, and a standard set of response options. So, for example, one question might be "In the past week, have you had abdominal pain?" and there might be four response options: "none at all", "a little", "quite a bit" or "very much". A related set of questions (e.g. about abdominal symptoms) are typically combined into a scale (based on the average scores of the component items). This scoring is codified in a scoring algorithm. The questionnaire, along with the algorithm for scoring the patients' responses into summary scores for analysis and reporting, is referred to as a PRO instrument or measure.

This approach draws on psychometric traditions by measuring complex variables broken down into their component parts. Each question (item) may ask about a specific issue, e.g. "have you had abdominal pain?"; this is the "item stem". The stem has a corresponding rating scale, which is referred to as the "response options". Generally, the response options are in the form of a Likert scale, i.e. where 1 = "none at all" and 4 = "very much". This step attaches a numerical value to each response. Items may be grouped with similar items, which together, tap into a larger construct, thereby providing a scale score. For example, the EORTC QLQ-C30 has five items assessing different aspects of physical functioning that are combined to provide a scale score for physical function. Alternatively, a scale may only be comprised of a single item. Any number of domains may be assessed in a single PRO instrument. In other words, the PRO instrument may assess only one domain (unidimensional) or several (multidimensional).

Given that HRQL is subjective and that ideally the patient should be the one to interpret each question, patients usually self-complete PRO instruments. This practice helps to reduce the bias that can be introduced when questions are discussed with other individuals. However, in some circumstances assistance may be necessary, such as when a patient is too fatigued or unable to read or speak the language of the questionnaire. As well as being quick and straightforward to use in research, PRO instruments are advantageous because they yield results that are directly comparable between studies. However, there are always limitations to the information that an instrument, or a battery of instruments, can provide.

## Choosing a PRO Instrument

There are a large number of instruments available to assess HRQL and other PROs, which makes it difficult for researchers to select appropriate instruments. This can be particularly problematic when more than one available instrument may seem applicable to the research context. To address this difficulty, researchers should consult clinicians, patients and the available literature to determine which issues are most relevant to their particular research question and treatment context [64]. Researchers should also consult databases such as PROQOLID [65], which catalogue a large number of PRO instruments, to help them to identify candidate instruments that assess the important domains of interest. These instruments should then be carefully reviewed to determine whether the questions they pose address the patients' issues in a meaningful way (i.e. whether they have content and face validity for the research context). The scoring method should also be reviewed to determine whether the instrument produces a score for the issue/s of importance to the research study. The literature should be consulted to determine whether the studies which

validated the instrument were methodologically sound (*refer to the* section "What Makes a Good Instrument" described in this chapter), or whether more validation work is needed. It is also important to consider whether criteria for a clinically important difference or clinical cut-offs have been established to allow for clinically meaningful interpretation of the data [66]. Finally, a pilot study in which patients from the population of interest self-complete the instrument can also be a useful to assess the suitability of an instrument.

**Key Questions to Consider When Selecting a PRO Instrument**

1. Is the PRO instrument intended for use in research or clinical practice?
2. Which issues are important to the particular research and treatment context?
3. Does the PRO instrument cover all the issues that matter in a given context?
4. Does the PRO instrument have evidence for important psychometric properties: validity, reliability, responsiveness, generalisability and interpretation?
5. Have clinically important difference criteria or cut-offs been established?

## What Makes a Good Instrument?

The scientific and methodologically rigorous development of a PRO instrument involves careful item selection informed by a literature review and both expert and patient input [3, 67]. Important psychometric properties include *validity*, *reliability*, *sensitivity*, *responsiveness* and *interpretability*. To decide whether an instrument is "good", the (1) conceptual and measurement models; (2) validity; (3) reliability; (4) responsiveness to change; (5) interpretability; (6) respondent and administrative burden; (7) alternative forms; and (8) cultural and language adaptations should be considered. An instrument should fit for purpose, i.e. appropriate for the intended clinical context and population. Importantly, when choosing an instrument for a particular population and context, check whether its psychometric properties should be determined in that population and context, particularly if that differs from the population and context for which the instrument was initially developed. It must also be acceptable to patients and feasible for them to self-complete. In both clinical practice and research, instruments should only be used that have been previously demonstrated to display these important psychometric properties.

## PRO Instruments for Ovarian Cancer Clinical Research: Core Cancer Instruments Versus Tumour Specific Modules

The two most widely used HRQL instruments in cancer clinical trials are the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30 [57]) and the Functional Assessment of Cancer Therapy-General (FACT-G [68]). Both instruments have ovarian cancer-specific modules that assess the HRQL of patients treated for ovarian cancer in clinical trials.

### EORTC Instruments

The QLQ-C30 is the core instrument of the EORTC's modular approach to HRQL assessment. It includes HRQL domains relevant to a range of cancer sites and treatment types. The EORTC conceptualised HRQL as multidimensional with at least three basic domains: physical functioning, including symptom experience and functional status; emotional functioning; and social functioning. It has 30 items which are incorporated into nine multi-item subscales: five functional (physical, role, cognitive, emotional, and social functioning); three symptom (fatigue, pain, and nausea/vomiting); and a global health status/HRQL scale, as well as six single items that assess dyspnoea, appetite loss, sleep disturbance, constipation, diarrhoea, and perceived

financial impact of disease and treatment. Response options for each item range from 1 (not at all) to 4 (very much) during the past week. The QLQ-C30 is designed to be used across different cancer populations and takes about 11 minutes to complete [68]. It is available in 96 languages. The QLQ-C30 is complemented by modules specific to particular cancers, such as ovarian cancer (QLQ-OV28). The core module facilitates comparison of HRQL cross cancers, and the disease-specific modules provide sensitivity for particular trials.

The QLQ-OV28 is the EORTC module specific to ovarian cancer. It is a 28-item questionnaire developed to assess the HRQL of women with ovarian cancer treated in clinical trials [69]. It consists of seven multi-item scales: abdominal/gastrointestinal symptoms (7 items), peripheral neuropathy (3 items), other chemotherapy side effects (7 items), hormonal/menopausal symptoms (2 items), body image (2 items), attitude to disease and treatment (3 items) and sexual function (4 items.) Response options for each item range from 1 (not at all) to 4 (very much) during the past week/4 weeks. It has been translated into 40 languages.

## FACIT Instruments

The FACT-G [68] is the core component within the Functional Assessment of Chronic Illness Therapy Measurement System (FACIT). The most recent version (version 4; 1997) includes 27 items intended for use with patients with any cancer type. The items cover four primary HRQL domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. Apart from domain scores, the instrument also generates a total HRQL score. Each item is rated on a scale from 0 (not at all) to 4 (very much) with respect the past 7 days. The FACT-G is available in 65 languages. In addition to the FACT-G, the FACIT suite has cancer-specific (e.g. ovarian), treatment-specific (e.g. neurotoxicity from systemic chemotherapy), and symptom-specific (e.g. fatigue) instruments.

The FACIT approach differs slightly from the EORTC modular system, where stand-alone modules are used in conjunction with the QLQ-C30. In the FACIT system, each of these disease, treatment and symptom-specific instruments implicitly includes the FACT-G instrument. For example, the FACT-O instrument contains all 27 questions from the FACT-G plus an additional 12 questions that relate specifically to ovarian cancer. The additional 12 items cover stomach bloating, weight loss, bowel control, vomiting, hair loss, appetite, body image, mobility, femininity, stomach cramps, interest in sex and reproductive concerns. The FACT-O instrument can be self-completed or used in an interview format and takes about 8–10 minutes to complete [70]. The FACT-O items are rated from 0 (not at all) to 4 (very much) during the past 7 days. It is available in 44 languages.

The FOSI [71, 72] and NCCN-FACT FOSI-18 [73] were developed to measure high priority symptoms and HRQL concerns in patients with advanced ovarian cancer. They consist of 8 and 18 items, respectively, of the FACT-O. The FOSI has the same response options as the FACT-G, and provides a single score. The FOSI-18 has advantages over the FOSI by including more symptoms and separating them into three subscales: disease-related symptoms (10 items), treatment side effects (5 items) and general functioning/well-being (3 items). Another divergence from the FOSI is that its 18 items are rated on a scale from 0 (not at all) to 10 (very much) during the past 7 days. The FOSI-18 can be self-completed or interviewer administered and takes 4–5 minutes to complete. It has been translated into 27 languages.

In addition, the FACIT suite includes a number of chemotherapy-specific questionnaires that are relevant to ovarian cancer contexts. These include the Functional Assessment of Cancer Treatment (FACT) Gynecology Oncologic Group Neurotoxicity Questionnaire (FACT&GOG-Ntx) [74] and the FACT-Taxane [75], which assess the impact of neuropathy on patients HRQL and the HRQL of patients receiving taxane containing chemotherapy, respectively. The FACT&GOG-

Ntx consists of 13 items, which are summed to produce a total neurotoxicity score and the FACT-Taxane has 16 items which score into two domains: Neurotoxicity (11 items) and taxane-induced symptoms (5 items).

## MOST: Measure of Ovarian Symptoms and Treatment concerns

While the EORTC-QLQ-C30 and QLQ-OV28 and the FACT-O and FOSI all assess ovarian cancer and treatment-related symptoms, their scoring algorithms either split the items into numerous scales (EORTC instruments) or generate scales by combining treatment side effects with other aspects of HRQL (FACIT instruments, except FOSI-18), which can dissipate effects [23]. Furthermore, the recall period for these PRO measures is a week, while the period between chemotherapy cycles is typically 3–4 weeks. The MOST [23] was developed to address these issues and provide a measure of overall symptom burden, as well as the benefits and adverse effects of chemotherapy that could be used as an endpoint in clinical trials of palliative chemotherapy for recurrent ovarian cancer.

There are two versions of the MOST. The original version (MOST-T35) contains 35 items, covering a mix of physical and psychological symptoms which may be caused by either disease and/or treatment side effects, other problems caused by treatment, and three aspects of well-being (physical, emotional, and overall) [76]. The MOST-T24 is a shorter symptom-focussed version containing 24 of the original 35 items [23]. These group into five psychometrically validated indexes for use as outcomes in clinical trials: abdominal symptoms (MOST-abdo, 2 items), chemotherapy-related symptoms (MOST-Chemo, 6 items), a group of 11 symptoms that may be caused by either ovarian cancer or its treatment (i.e. disease or treatment, MOST-DorT, 11 items), psychological symptoms (MOST-Psych, 2 items), and well-being (MOST-well-being, 3 items). In both versions, response options for each item range from 0 (no problem or best possible) to 10 (worst possible) during the past 3–4 weeks. The MOST is the newest ovarian cancer-specific instrument and has been translated into six languages so far.

The MOST change [76] is an alternate form of the MOST that asks patients to report on their perceived change since beginning chemotherapy by asking patients to "circle the number that best represents how you feel now, *compared to* how you felt before starting this chemotherapy treatment 6 to 8 weeks ago". The MOST change was developed to allow the estimation of the minimally important difference [66, 77]. It consists of 35 items corresponding to the 35 items in MOST-T35 (which include the 24 items in MOST-T24). Response options for each item range from 1 (much better) to 5 (much worse). The MOST change has also been translated into six languages.

## On-Going Clinical Trials in Ovarian Cancer

Three clinical trials databases were searched (ClinicalTrials.gov, EU Clinical Trials Register, ANZCTR) to identify ongoing clinical trials in ovarian cancer. Internationally, there are currently 73 active ovarian cancer clinical trials collecting PROs from more than 28,200 women. Many of these studies are multi-national collaborations, with the majority coordinated in the UK, Italy, the USA and Australia. The treatments under investigation are predominately chemotherapy (18) and targeted therapies (46) for women with advanced ovarian cancer. PROs being assessed in these trials include overall HRQL; symptoms and treatment side effects; anxiety and depression; and functioning domains. Of the 47 trials that list the PRO instruments they include, 21 are using the EORTC QLQ-C30 (18 in combination with the QLQ-OV28), 13 are using the FACT-O, 4 include an ovarian cancer symptom index (NCCN-FACT FOSI-18), 3 use the MOST, and 12 include other measures not specific to ovarian cancer (e.g. the EQ-5D; NCI-PRO-CTCAE; HADS; SF-36). Nine trials are looking at PROs as a primary endpoint in interventions examining chemotherapy regimens (2),

counselling (2), exercise (1), mindfulness (1), nutrition (1), pain relief medication (1), and shared decision-making (1).

## Conclusions and Recommendations

The main treatment modality for ovarian cancer is cytoreductive surgery and chemotherapy. Unfortunately, the majority of women are diagnosed at an already advanced stage and less than half of these women will survive beyond 5 years. Following first-line treatment, many women develop recurrence and may undergo repeated cycles of chemotherapy. The assessment of HRQL throughout each phase of treatment and survivorship is essential, not only to guide improvements in clinical practice, but also to inform treatment decision-making by providing information about the risks and benefits of treatments.

Given the aggressiveness of ovarian cancer and its treatments, it is imperative that patients' HRQL be considered in treatment decision-making at patient and policy levels and assessed in clinical trials and potentially in routine clinical care. Both physical and psychological symptoms as well as functioning impairments affect HRQL throughout the entire disease and treatment trajectory. The assessment of symptoms, functioning and HRQL is useful during patient consultations and survivorship phases to allow for the early detection and management of the issues that impact patients' HRQL as well as to identify and support their unmet needs. Clinicians should discuss the likely short- and long-term benefits and harms of treatments on HRQL with their patients. The provision of supportive care both during and after treatment may also help to manage symptoms and improve the HRQL of women with ovarian cancer. Consideration should also be given to the HRQL and unmet needs of the women's partners and/or caregivers.

HRQL research and the implementation of PROs in clinical practice is a growing field, which is evidenced by the 73 ongoing clinical trials in ovarian cancer that include PRO endpoints. Importantly, the inclusion of PRO endpoints in clinical trials requires careful consideration. However, reviews indicate that many past ovarian cancer trials lacked prespecified PRO hypotheses and guidance on PRO administration as well as shortcomings in the analyses and interpretation of PRO data [10, 78]. These issues can be addressed by complying with PRO guidance during trial protocol development, selecting appropriate PRO measures to match clinically motivated PRO hypotheses, minimising rates of avoidable missing PRO data during trial conduct, and transparently reporting PRO findings [79]. To facilitate international best practice standards of PRO inclusion in trial protocols, the SPIRIT-PRO was released in 2018 [80]. SPIRIT-PRO provides an international, consensus-based checklist that provides useful guidance on the minimum set of items that should be included in the PRO sections of clinical trial protocols.

In this chapter we provided a brief overview of the evidence for the impact of ovarian cancer and its treatment on HRQL to date, discussed issues to consider when using PROs in ovarian cancer research and clinical settings and summarised ongoing ovarian cancer clinical trials. Several PRO measures are available for use and the appropriate selection of PRO instruments should always be guided by the specific research question and patient/treatment context. Information about specific PRO instruments, including information about their psychometric properties, can be found on the Mapi Research Trust PROQOLID website. For further information and resources please visit the websites for the Sydney Quality of Life Office, University of Sydney, and The International Society of Quality of Life Research.

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