Gynecologic Oncology Reports 50 (2023) 101293

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Health state utility and health-related quality of life measures in patients with advanced ovarian cancer

Ruby M. van Stein [a], Florine J. Hendriks [b], Valesca P. Retèl [c,d], Cor D. de Kroon [b], Christianne A.R. Lok [a], Gabe S. Sonke [e], Kelly M. de Ligt [c,1], Willemien J. van Driel [a,1,*]

[a] Department of Gynecologic Oncology, Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
[b] Department of Gynecology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands
[c] Department of Psychosocial Research and Epidemiology, Department of Psychosocial Research, Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
[d] Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands
[e] Department of Medical Oncology, Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

ARTICLE INFO

Keywords:
Health-related quality of life
Health state utility
Ovarian cancer

ABSTRACT

Purpose: Measuring health-related quality of life (HRQoL) in ovarian cancer patients is critical to understand the impact of disease and treatment. Preference-based HRQoL measures, called health state utilities, are used specifically in health economic evaluations. Real-world patient-reported data on HRQoL and health state utilities over the long-term course of ovarian cancer are limited. This study aims to determine HRQoL and health state utilities in different health states of ovarian cancer.

Methods: This cross-sectional, multicenter study included patients with stage III-IV ovarian cancer in six health states: at diagnosis, during chemotherapy, after cytoreductive surgery (CRS), after chemotherapy, in remission, and at first recurrence. HRQoL was measured using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire C30, and the ovarian cancer-specific module OV28. Health state utilities were assessed using the EuroQol five-dimension five-level (EQ-5D-5L) questionnaire. Descriptive analyses were performed for each health state.

Results: Two hundred thirty-two patients participated, resulting in 319 questionnaires. Median age was 66 years. The lowest HRQoL was observed during chemotherapy and shortly after CRS. Physical and role functioning were most affected and the highest symptom prevalence was observed in the fatigue, nausea, pain, dyspnea, gastrointestinal, neuropathy, attitude, and sexuality domains. Patients in remission had the best HRQoL. Mean utility values ranged from 0.709 (±0.253) at diagnosis to 0.804 (±0.185) after chemotherapy.

Conclusions: This study provides clinicians with a valuable resource to aid in patient counseling and clinical decision-making. The utilities, in particular, are crucial for researchers conducting economic analyses to inform policy decisions.

1. Introduction

In 2020, approximately 314.000 women worldwide were diagnosed with ovarian cancer (Sung et al., 2021). Due to the lack of specific symptoms, most patients present with advanced disease (International Federation of Gynecology and Obstetrics (FIGO) stage III or IV). Despite multimodality treatment, the majority of these patients relapse within two years (Reid et al., 2017). Importantly, treatment and disease burden have a significant impact on health-related quality of life (HRQoL). Affected women face a range of challenges, including alterations in physical function, psychological distress, social problems, and sexual dysfunction (Sun et al., 2007; Chase and Wenzel, 2011).

With the growing emphasis on patient-centered care, HRQoL as assessed by patient-reported outcome measures (PROMs) has become increasingly important in the evaluation of therapeutic interventions. HRQoL assessments evaluate the patients' perceptions of the impact of disease and treatment on their daily lives and overall satisfaction. These data help guide clinical decision-making by weighing the potential

* Corresponding author.
E-mail address: w.v.driel@nki.nl (W.J. van Driel).
[1] Authors contributed equally.

https://doi.org/10.1016/j.gore.2023.101293
Received 17 July 2023; Received in revised form 9 October 2023; Accepted 14 October 2023
Available online 17 October 2023

benefits of therapy against its potential impact (Chase and Wenzel, 2011). Furthermore, HRQoL is an essential component of health economic evaluations. Such evaluations determine the relationship between the health benefits and costs of an intervention, and guide management decisions on the allocation of healthcare resources and reimbursement. To incorporate quality of life into economic evaluations, generic preference-based measures are used, which provide utilities that estimate an individuals' valuation of a given health state (Wolowacz et al., 2016). Health state utilities are distinct from HRQoL measures and are required to calculate the quality-adjusted life year (QALY) that expresses the effectiveness in cost-effectiveness analyses (Wolowacz et al., 2016).

PROMs have been included in various clinical trials and observational studies to measure HRQoL in the context of ovarian cancer (Kumar et al., 2019; Wilson et al., 2018; Lee et al., 2022; Koole et al., 2019; Kim et al., 2022; Kehoe et al., 2015; Fagotti et al., 2016; Sundar et al., 2022). However, there is a paucity of studies assessing HRQoL in real-world patient populations and across important health states during the long-term course of the disease, such as at primary diagnosis, during treatment, in a disease-free status, and at recurrence. In addition, although some studies have reported utilities in ovarian cancer, these are often not patient-reported (but e.g. reported by clinical experts), based on small sample sizes, assessed in limited health states, or assessed in clinical trial settings that may not accurately represent real-world settings (Bristow et al., 2007; Havrilesky et al., 2008; Lesnock et al., 2011; Forde et al., 2016; Uppal et al., 2012; Stein et al., 2007; Havrilesky et al., 2009; Friedlander et al., 2021; Mirza et al., 2016; van de Vrie et al., 2017). Therewith, health economic analyses often have to rely on synthesis of QoL data, which is not optimal.

In summary, there are limited data on HRQoL and health state utilities in the context of ovarian cancer. A comprehensive assessment of HRQoL in different health states from diagnosis to first recurrence will contribute to a better understanding of the disease burden and symptom prevalence associated with ovarian cancer treatment to guide shared decision-making. Furthermore, an adequate estimation of health state utilities is essential for cost-effectiveness assessments required in the context of clinical implementation of novel therapies, and to inform health care providers about the cost-effectiveness of existing therapies. Therefore, the aim of this study is to determine HRQoL and health state utilities in a real-world sample of patients with advanced ovarian cancer in different health states. Ultimately, the combination of these data provides an opportunity to develop a mapping algorithm to enable the use of available HRQoL data in the absence of health state utilities.

2. Materials and methods

2.1. Study design

This observational, cross-sectional study measured HRQoL and health state utilities in patients with advanced ovarian cancer. The study was conducted between June 2020 and March 2023 at the Netherlands Cancer Institute - Antoni van Leeuwenhoek in Amsterdam and Leiden University Medical Center in Leiden, both specialized cancer centers in the Netherlands. The institutional review boards of both institutions approved the study (IRBd19-337; N21.081). Written informed consent was obtained from all participants.

2.2. Study participants

Eligible patients were ≥18 years of age, had FIGO stage III-IV epithelial ovarian cancer, and were able to read and write Dutch or English. Patients were eligible to participate in the health states depicted in Fig. 1. These states reflect the disease and treatment course of advanced ovarian cancer from diagnosis to first recurrence. Patients could participate in one or more of the health states. Study recruitment involved systematic screening of outpatient and surgical schedules at both centers. All eligible patients who visited the hospital for a consultation or had a telephone appointment were approached for participation.

2.3. Standard of care

Treatment of newly diagnosed advanced ovarian cancer includes cytoreductive surgery (CRS) and platinum-based chemotherapy. In the participating centers, CRS is typically performed through an open laparotomy procedure and routinely encompasses a hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and, when necessary, the resection of other structures and peritonectomy. Routine treatment included primary CRS with six cycles of adjuvant chemotherapy. If complete primary CRS was not considered feasible due to disease extent, it was decided during the multidisciplinary team meeting to start with neo-adjuvant chemotherapy.. Standard chemotherapy consisted of six cycles of carboplatin (area under the curve of 5 to 6 mg/mL/min) and paclitaxel (175 mg/m^2 of body-surface area) administered in a 3-week schedule. As an alternative to adjuvant cycles of intravenous chemotherapy following primary CRS, adjuvant cycles of intravenous paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel were allowed according to the Armstrong regimen. Carboplatin monotherapy or carboplatin and weekly paclitaxel were administered when indicated. Several patients received hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin (100 mg/m^2) for 90 min as an adjunct to CRS. Patients with high-grade tumors harboring pathogenic BRCA1/2 mutations were candidates for adjuvant poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)-inhibitor therapy. After disease recurrence, treatment consisted of chemotherapy, bevacizumab, radiotherapy, secondary CRS, PARPi, and/or hormonal therapy according to local protocol and tailored to individual preference.

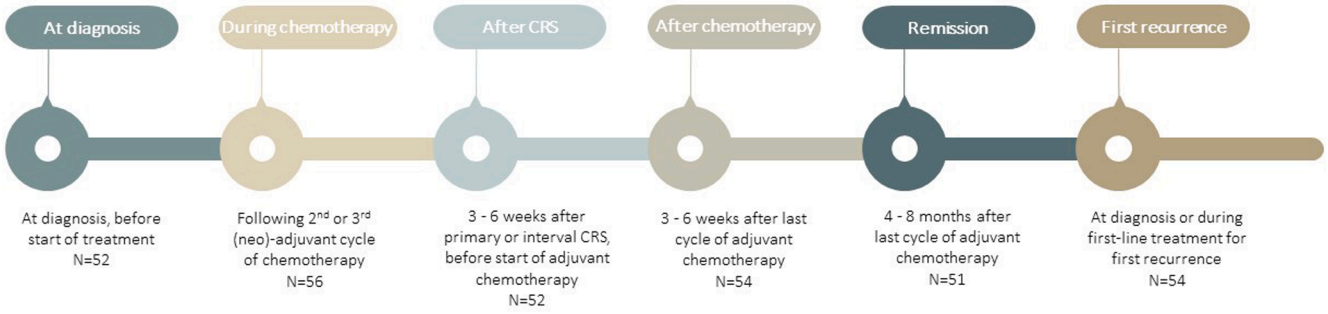

Fig. 1. Health states. Patients were eligible to participate during one of the health states depicted in this figure. These states reflect the disease and treatment course of advanced ovarian cancer. Patients could participate in one or more health states.

2.4. Cross-sectional survey

Demographic, diagnostic, and clinical characteristics were retrieved from the electronic medical record. Participants were asked to complete a survey that included three validated questionnaires: the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), an ovarian cancer-specific questionnaire module (EORTC QLQ-OV28), and the five-level EuroQol five-dimension questionnaire (EQ-5D-5L). Sociodemographic characteristics (highest completed level of education, current occupation) were also collected by survey. Participants completed the paper-and-pencil survey and returned it by mail or handed it in at the hospital.

The EORTC QLQ-C30 and QLQ-OV28 are standardized and validated instruments for the assessment of HRQoL in ovarian cancer patients and are recommended for use in clinical and research settings (Aaronson et al., 1993; Greimel et al., 2003). The QLQ-C30 is a 30-item multidimensional, cancer-specific questionnaire that includes five multi-item function scales (physical, role, cognitive, emotional, and social), three multi-item symptom scales (fatigue, nausea and vomiting, and pain), five single-item symptom scales (dyspnea, insomnia, loss of appetite, constipation, and diarrhea), a financial impact question, and a two-item global QoL scale (Aaronson et al., 1993). A 4-point Likert scale is used for all items except for the global health status/QoL scale, which uses a 7-point scale. The QLQ-OV28 is a 28-item ovarian cancer-specific questionnaire designed to complement the QLQ-C30 (Greimel et al., 2003). It comprises seven multi-item symptom scales assessing abdominal or gastrointestinal symptoms, peripheral neuropathy, hormonal or menopausal symptoms, other chemotherapy side effects, body image, attitude toward disease or treatment, and sexuality. A 4-point Likert response scale is used for all items on the QLQ-OV28. All QLQ-C30 and QLQ-OV28 data were scored and transformed linearly to a scale of 0–100 according to validated scoring instructions by the EORTC Quality of Life Group (Fayers et al., 2001). For the functional and global QoL scales, a higher score represents a better level of functioning. For the symptom scales, a higher score represents a higher level of symptoms. The QLQ-C30 summary score was calculated as the mean of all scale scores except global QoL and financial impact, with higher scores representing better HRQoL (Giesinger et al., 2016). Recently, clinical relevance thresholds have been developed for all scales of the QLQ-C30 to facilitate clinical interpretation of the scores (Giesinger et al., 2020).

The EQ-5D-5L is a standardized instrument developed by the EuroQol Group for the generic preference-based measurement of HRQoL. This questionnaire provides utilities that reflect preference for a given health-related outcome on a numerical scale (1.0 represents full health, 0.0 represents death) (Wolowacz et al., 2016). The EQ-5D-5L has become the cornerstone of health technology assessment (Longworth and Rowen, 2013). The questionnaire consists of the EQ-5D-5L descriptive system and the EQ visual analog scale (EQ-VAS). The descriptive system includes five dimensions: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression, all with five levels: no problems, mild problems, moderate problems, severe problems, and extreme problems. The five responses can be scored into a single index utility using the Index Calculator, which has been validated for the Dutch general population (Versteegh et al., 2016). The EQ-VAS records a patients' self-rated health on a vertical visual analog scale, with endpoints labeled from 'the best health you can imagine' (100) to 'the worst health you can imagine' (0). The EQ-VAS and the EQ-5D Index (utility) serve distinct conceptual purposes. While the EQ-5D Index assigns a value to an EQ-5D profile based on the preferences of the general population of a country/region for different health states, representing the societal perspective, the EQ-VAS reflects the patients' own perspective.

2.5. Statistical analyses

Sociodemographic and clinical characteristics were described. Analyses of the EORTC QLQ-C30, QLQ-OV28 and the EQ-5D-5L data were described for each health state, with standard deviations (SD) calculated around the mean QLQ-C30, QLQ-OV28, EQ-5D utility and EQ-VAS scores. For the QLQ-C30 scales, clinical importance thresholds were applied in each health state to assess which functional and symptom scales were affected (Giesinger et al., 2020). The Statistical Package for the Social Sciences (version 27.0, SPSS, Inc.) was used.

3. Results

3.1. Participants

A total of 232 individual patients participated, contributing to a total of 319 questionnaires. Among these participants, 173 patients participated in one health state, 37 patients in two different health states, and 22 patients participated in more than two (ranging from 3 to 5) health states. The number of participants for each health state was 52 at diagnosis, 56 during chemotherapy, 52 after CRS, 54 after chemotherapy, 51 in remission, and 54 at first recurrence. Over 98 % of the invited patients agreed to participate, although 18 % did not return the completed questionnaires. Demographic and clinical data of the participants are presented in Table 1. The median age of the participants was 66 years. Most patients (70.2 %) had FIGO stage III ovarian cancer. Nearly all participants (96.8 %) were white. Most patients were in a relationship (78.4 %) and had children (77.6 %). More than one third of the patients (41.4 %) had a higher professional or (post)academic education.

3.2. Item compliance

All items except the sexuality items showed good compliance with a maximum of 1.5 % missing values. Items about sexuality were missing in 6.4 %. In ten surveys, the EORTC QLQ-C30 and QLQ-OV28 questionnaires were completed, but the EQ-5D-5L questionnaire was not (reason unknown).

3.3. Outcomes

3.3.1. HRQoL

Descriptive statistics of the EORTC QLQ-C30 and QLQ-OV28 scores for each health state are tabulated in Tables 2 and 3. The lowest overall C30 summary score and mean global health status were observed during chemotherapy (71.7 and 63.5) and after CRS (70.5 and 59.1), respectively. Also, in both health states, thresholds for clinical importance were exceeded for physical and role functioning, and fatigue, nausea, pain, and dyspnea (Giesinger et al., 2020). Similar functional and symptom domains were worse than the threshold of clinical importance in the recurrent health state, except for the role functioning and pain scales. Patients in remission had the best QLQ-C30 outcomes (overall C30 summary score, 84.1; mean global health status, 77.5), with none of the functional or symptom scales exceeding the threshold for clinical relevance (Giesinger et al., 2020).

As measured by the QLQ-OV28, the highest level of symptomatology was again seen during chemotherapy and after CRS. Patients at baseline and in remission had the best QLQ-OV28 outcomes. Abdominal symptoms were most common at baseline, during first-line treatment, and at first recurrence. Neuropathy symptoms were observed in all health states except at diagnosis. Attitude to disease/treatment and sexual symptoms were commonly reported in all health states.

3.3.2. Health state utility

The EQ-5D-5L descriptive system is shown in Table 4a. In each health state, the pain/discomfort dimension was most affected and the self-care dimension was least affected. Table 4b shows the EQ-5D index and EQ-VAS outcomes for each health state. The highest mean utility was observed after chemotherapy (0.804). The lowest mean utility was observed at diagnosis (0.709) and after CRS (0.710).

Table 1
Patient and disease characteristics.

Parameter	1. At diagnosis (n = 52)	2. During chemo (n = 56)	3. After CRS (n = 52)	4. After chemo (n = 54)	5. In remission (n = 51)	6. Recurrence (n = 54)
Age, median (IQR) – years	64 (56–63)	65 (61–67)	66 (61–67)	67 (61–67)	67 (62–68)	65 (61–66)
Marital status – no. (%)						
Married	22 (48.9)	31 (56.4)	32 (64.0)	28 (52.8)	31 (63.2)	31 (57.4)
Cohabiting relationship	10 (22.2)	8 (14.5)	10 (20.0)	11 (20.7)	8 (16.3)	9 (1.7)
Non-cohabiting relationship	2 (4.4)	/	2 (4.0)	1 (1.9)	2 (4.1)	2 (3.7)
Widowed/single	11 (24.4)	16 (29.1)	6 (12.0)	13 (24.5)	8 (16.3)	12 (22.2)
Unknown	7	1	2	1	2	/
Children – no. (%)						
Yes						
Living on their own	26 (56.5)	29 (52.7)	33 (67.3)	36 (69.2)	32 (66.7)	37 (68.5)
Living at home	6 (13.0)	12 (21.8)	5 (10.2)	7 (13.5)	7 (14.6)	6 (11.1)
No	14 (30.4)	14 (25.4)	11 (22.4)	9 (17.3)	9 (18.7)	11 (20.4)
Unknown	6	1	3	2	3	/
Ethnicity – no. (%)						
White	46 (93.8)	55 (98.2)	50 (98.0)	52 (96.3)	49 (96.1)	53 (98.1)
Black	1 (2.0)	/	/	/	/	1 (1.9)
Asian	2 (4.1)	1 (1.8)	1 (2.0)	2 (3.7)	2 (3.9)	/
Unknown	3	/	1	/	/	/
Education level – no. (%)						
Primary education	2 (4.9)	2 (3.6)	1 (2.3)	1 (2.0)	2 (4.1)	5 (9.4)
Secondary education	8 (19.5)	12 (21.8)	10 (23.2)	10 (19.6)	13 (26.5)	14 (26.4)
Vocational education	2 (4.9)	3 (5.4)	3 (7.0)	3 (5.9)	2 (4.1)	1 (1.9)
Secondary vocational education	13 (31.7)	17 (30.9)	10 (23.2)	15 (29.4)	11 (22.4)	11 (20.8)
Higher professional education	14 (34.1)	14 (25.4)	18 (41.9)	16 (31.4)	17 (34.7)	13 (24.5)
(Post)academic education	2 (4.9)	7 (12.7)	1 (2.3)	6 (11.8)	4 (8.2)	9 (17.0)
Unknown	11	1	9	3	2	1
Current occupation – no. (%)						
Full or part-time job/Study/Self-employed	19 (40.4)	19 (33.9)	7 (14.9)	11 (21.6)	14 (28.0)	13 (24.0)
Unemployed/Retired/ (Payed) sick Leave	28 (59.6)	37 (66.1)	40 (85.1)	40 (78.4)	36 (72.0)	41 (76.0)
Unknown	5	/	5	3	1	/
Comorbidity * – no. (%)						
No comorbidity	41 (78.9)	35 (62.5)	32 (61.5)	40 (74.1)	44 (86.3)	44 (81.5)
1	11 (21.1)	18 (32.1)	17 (32.7)	11 (20.4)	6 (11.8)	7 (13.0)
≥2	/	3 (5.4)	3 (5.8)	3 (5.6)	1 (1.9)	3 (5.6)
FIGO classification – no. (%)						
II	/	/	/	/	/	2 (3.7)
III	46 (88.5)	30 (53.6)	44 (84.6)	40 (74.1)	37 (72.5)	27 (50.0)
IV	6 (11.5)	26 (46.4)	8 (15.4)	14 (25.9)	14 (27.5)	25 (46.3)
Cytoreductive surgery – no. (%)						
No CRS (yet)	52 (100)	39 (69.6)	/	1 (1.9)	/	/
Primary CRS	/	7 (12.5)	30 (57.7)	29 (53.7)	24 (47.1)	10 (18.5)
Interval CRS	/	10 (17.9)	22 (42.3)	24 (44.4)	27 (52.9)	44 (81.5)
HIPEC – no. (%)		3 (5.4)	32 (61.5)	24	20 (39.2)	15 (27.8)
Chemotherapy cycles^– no. (%)						
<6		56 (100)	50 (96.2)	2 (3.7)	2 (3.9)	3 (5.6)
6		/	2 (3.8)	50 (92.6)	48 (94.1)	49 (90.7)
>6		/	/	2 (3.7)	1 (2.0)	2 (3.7)
PARPi maintenance – no. (%)				1 (1.9)	9 (17.6)	6 (11.1)
Current recurrence treatment – no. (%)						
Chemotherapy						18 (33.3)
Chemotherapy and bevacizumab						1 (1.9)
PARPi						5 (9.3)
Hormonal therapy						4 (7.4)
No treatment (yet)						26 (4.8)
Median recurrence-free survival (IQR) † – days						376 (477–961)

Abbreviations: CRS cytoreductive surgery; IQR interquartile range; HIPEC hyperthermic intraperitoneal chemotherapy; PARPi Poly (ADP-ribose) polymerase inhibitor; NA not applicable.
* Number of categories according to Charlson Comorbidity Index.
^First-line treatment for primary diagnosis.
† Calculated from last cycle of chemotherapy.

Table 2
EORTC-QLQ-C30.

	1. At diagnosis (n = 52)	2. During chemo (n = 56)	3. After CRS (n = 52)	4. After chemo (n = 54)	5. In remission (n = 51)	6. Recurrence (n = 54)
Overall QLQ-C30 summary score (±SD)	78.5 (16.3)	71.7 (15.6)	70.5 (14.5)	82.2 (12.0)	84.1 (10.9)	76.3 (15.2)
Global health status, mean (±SD)	66.0 (21.4)	63.5 (19.5)	59.1 (15.8)	69.3 (15.6)	77.5 (14.9)	69.0 (19.9)
Functional scales †, mean (±SD)						
Physical functioning	84.5 (18.4)	**74.1 (17.7)**	**65.3 (18.3)**	**79.0 (17.7)**	84.4 (14.3)	**75.8 (23.7)**
Role functioning	76.3 (27.3)	**57.3 (31.9)**	**44.1 (30.5)**	69.4 (26.6)	79.4 (26.4)	67.6 (29.0)
Emotional functioning	**62.0 (25.3)**	73.5 (23.9)	75.3 (18.4)	80.9 (18.6)	80.0 (18.3)	72.7 (21.1)
Cognitive functioning	80.1 (24.5)	76.8 (23.9)	81.7 (23.4)	77.8 (24.2)	75.5 (27.4)	76.2 (26.8)
Social functioning	80.7 (25.2)	67.6 (26.7)	63.1 (24.6)	81.8 (19.5)	80.4 (24.9)	80.4 (24.9)
Symptom scales *, mean (±SD)						
Fatigue	28.2 (25.5)	**45.7 (24.2)**	**49.4 (24.7)**	32.9 (23.4)	26.1 (19.3)	**39.9 (24.8)**
Nausea	6.4 (13.3)	**11.8 (17.2)**	**10.6 (20.6)**	4.0 (11.6)	2.9 (7.2)	**11.7 (21.4)**
Pain	**29.2 (25.5)**	**26.8 (27.1)**	**35.9 (23.0)**	13.3 (20.3)	16.0 (18.5)	23.5 (25.2)
Dyspnea	13.5 (22.1)	**25.4 (29.4)**	**17.3 (26.8)**	**19.7 (23.8)**	14.4 (20.3)	**17.9 (26.5)**
Insomnia	37.8 (31.7)	32.1 (34.5)	30.1 (28.2)	21.6 (24.4)	25.5 (28.0)	33.9 (35.1)
Appetite loss	24.4 (31.0)	29.1 (32.1)	33.3 (31.7)	8.6 (19.6)	3.3 (15.3)	14.8 (26.4)
Constipation	12.4 (25.8)	30.9 (32.6)	20.5 (29.6)	13.2 (25.6)	15.0 (27.7)	19.7 (28.6)
Diarrhea	12.2 (23.8)	16.4 (27.1)	13.5 (21.1)	4.9 (18.8)	3.3 (10.0)	11.7 (26.0)
Financial difficulties	9.1 (22.2)	8.5 (22.4)	5.1 (16.7)	4.9 (17.6)	8.5 (18.7)	7.4 (19.1)

All item responses are linearly converted to a 0–100 scale.
Bold: Functional scales and symptom scales that exceed the thresholds for clinical importance.
† A high score represents a high level of functioning.
* A high score represents a high level of symptomatology or problems.

Table 3
EORTC-QLQ-OV28.

	1. At diagnosis (n = 52)	2. During chemo (n = 56)	3. After CRS (n = 52)	4. After chemo (n = 54)	5. In remission (n = 51)	6. Recurrence (n = 54)
Symptom scales †, mean (±SD)						
Abdominal/gastro-intestinal	30.3 (22.0)	32.3 (18.3)	30.8 (17.3)	17.5 (14.8)	16.8 (13.4)	27.2 (20.9)
Neuropathy	8.3 (17.2)	37.7 (32.1)	23.9 (24.6)	37.2 (28.6)	31.9 (26.5)	29.7 (25.8)
Other chemotherapy side effects	13.7 (14.4)	35.3 (19.6)	21.3 (15.1)	24.4 (18.6)	17.8 (16.1)	16.2 (14.6)
Hormonal/menopausal	14.4 (24.3)	17.6 (26.1)	17.6 (23.2)	15.7 (24.3)	19.6 (28.2)	25.5 (29.5)
Body image	23.7 (27.7)	34.2 (32.5)	39.1 (32.1)	29.9 (28.3)	18.9 (23.2)	25.6 (27.6)
Attitude to disease/treatment	52.1 (27.3)	61.9 (24.9)	59.0 (21.5)	51.9 (23.9)	52.1 (25.7)	58.9 (22.5)
Sexuality	85.0 (25.1)	92.6 (15.0)	92.5 (19.0)	90.4 (17.9)	79.8 (24.5)	84.6 (21.0)

All item responses are linearly converted to a 0–100 scale.† A high score represents a high level of symptomatology or problems.

4. Discussion

This cross-sectional, observational study reports HRQoL and health state utilities in patients with advanced ovarian cancer in six health states, reflecting the disease and treatment course. The worst QLQ-C30 and QLQ-OV28 scores were observed in patients during chemotherapy and after CRS. Physical and role functioning were most affected. The highest symptom prevalence was observed in the fatigue, nausea, pain, dyspnea, gastrointestinal, neuropathy, attitude, and sexuality domains. Patients who had completed first-line treatment had the best HRQoL. Mean utility was highest after chemotherapy and lowest at time of diagnosis and after CRS.

4.1. Results in context of published literature

4.1.1. HRQoL

The importance of HRQoL assessment is well recognized in both clinical and research settings. However, most reports of PROMS on HRQoL in the context of ovarian cancer are limited to specific treatment regimens, settings, or clinical trials. Relatively high C30 summary scores and global health status scores, both >10.0 points higher than those reported in the literature, were observed in the subset of patients in our study who were assessed at the time of primary diagnosis (Kim et al., 2022; Kehoe et al., 2015; Fagotti et al., 2016). This could be attributed to potential differences in patient characteristics or sociodemographics between the study populations, but information on these parameters was not available in detail in these reports. Furthermore, the Dutch general population tends to report better HRQoL compared to many other countries (Nolte et al., 2019). Previous research suggests that HRQoL typically declines shortly after CRS and during chemotherapy, likely due to treatment-related toxicities and adverse events (Kim et al., 2022; Fagotti et al., 2016; Sundar et al., 2022). Nevertheless, HRQoL scores have been shown to improve over time in several domains improve over time, likely as a result of treatment benefits (Kumar et al., 2019; Sundar et al., 2022). Our results are consistent with these findings, as patients who completed first-line treatment and achieved remission had the most favorable HRQoL outcomes. When relapse occurs, patients often experience a variety of symptoms related to disease progression and accumulated toxicities from chemotherapy or other therapies. Consistent with our findings, the Gynecologic Cancer Inter Group (GCIG)-Symptom Benefit study showed that patients with recurrence experience a substantial burden of HRQoL. The study found that approximately 15 % of participants reported a positive impact on HRQoL following palliative chemotherapy (Lee et al., 2022).

To effectively treat and support patients with ovarian cancer and enhance their overall well-being and HRQoL, it is important to have a comprehensive understanding of the wide range of symptoms that they may experience. Our findings regarding the most prevalent

Table 4a
EQ-5D-5L: descriptive system.

Domain	1. At diagnosis (n = 51)	2. During chemo (n = 54)	3. After CRS (n = 50)	4. After chemo (n = 52)	5. In remission (n = 49)	6. Recurrence (n = 53)
Mobility - no. (%)						
No problems	40 (78.4)	28 (51.9)	26 (52.0)	31 (59.6)	31 (63.3)	36 (67.9)
Slight problems	5 (9.8)	15 (27.8)	13 (26.0)	11 (21.2)	8 (16.3)	10 (18.9)
Moderate problems	3 (5.9)	7 (13.0)	9 (18.0)	6 (11.5)	8 (16.3)	2 (3.8)
Severe problems	3 (5.9)	4 (7.4)	2 (4.0)	4 (7.7)	2 (4.1)	4 (7.5)
Unable to walk about	0	0	0	0	0	1 (1.9)
Self-care - no. (%)						
No problems	46 (90.2)	49 (90.7)	41 (82.0)	51 (98.1)	47 (96.0)	49 (92.5)
Slight problems	2 (3.9)	4 (7.4)	7 (14.0)	0	1 (2.0)	3 (5.7)
Moderate problems	3 (5.9)	1 (1.9)	2 (4.0)	0	1 (2.0)	0
Severe problems	0	0	0	1 (1.9)	0	0
Unable to wash or dress	0	0	0	0	0	1 (1.9)
Everyday activities - no. (%)						
No problems	25 (49.0)	16 (29.6)	10 (20.0)	25 (48.1)	26 (53.1)	23 (43.4)
Slight problems	17 (33.3)	13 (24.1)	13 (26.0)	16 (30.8)	12 (24.5)	14 (26.4)
Moderate problems	5 (9.8)	19 (35.2)	16 (32.0)	8 (15.4)	6 (12.2)	10 (18.9)
Severe problems	3 (5.9)	4 (7.4)	8 (16.0)	3 (5.8)	5 (10.2)	4 (7.5)
Unable to do usual activities	1 (2.0)	2 (3.7)	3 (6.0)	0	0	2 (3.8)
Pain/discomfort - no. (%)						
No pain	12 (23.1)	13 (24.1)	10 (20.0)	21 (40.4)	15 (30.6)	17 (32.1)
Slight pain	27 (51.9)	28 (51.9)	27 (54.0)	23 (44.2)	26 (53.1)	29 (54.7)
Moderate pain	10 (19.2)	11 (20.4)	11 (22.0)	6 (11.5)	5 (10.2)	5 (9.4)
Severe pain	2 (3.8)	2 (3.7)	2 (4.0)	1 (1.9)	3 (6.1)	2 (3.8)
Extreme pain	1 (1.9)	0	0	1 (1.9)	0	0
Anxiety/depression - no. (%)						
Not anxious	16 (30.8)	25 (46.3)	25 (50.0)	31 (59.6)	25 (51.0)	26 (49.1)
Slightly anxious	20 (38.5)	13 (24.1)	13 (26.0)	15 (28.8)	16 (32.7)	18 (34.0)
Moderately anxious	4 (7.7)	14 (25.9)	10 (20.0)	6 (11.5)	6 (12.2)	6 (11.3)
Severely anxious	10 (19.2)	1 (1.9)	2 (4.0)	0	2 (4.1)	3 (5.7)
Extremely anxious	2 (3.8)	1 (1.9)	0	0	0	0

Table 4b
EQ-5D-5L: EQ index and EQ-VAS.

	1. At diagnosis (n = 51)	2. During chemo (n = 54)	3. After CRS (n = 50)	4. After chemo (n = 52)	5. In remission (n = 49)	6. Recurrence (n = 53)
Total utility (EQ-5D Index)†, mean (±SD)	0.709 (0.253)	0.727 (0.174)	0.710 (0.182)	0.804 (0.185)	0.776 (0.209)	0.761 (0.207)
EQ-VAS*, mean (±SD)	64.3 (23.2)	67.2 (16.7)	59.3 (17.5)	69.3 (14.5)	75.8 (13.0)	69.6 (19.2)

† This variable contains the values of the EQ-5D-5L index values on the basis of the NL set of weights. Ranging from 0.0 (representing death) to 1.0 (representing full health).
* Ranging from 0.0 'the worst health you can imagine' to 100.0 'the best health you can imagine'.

symptomatology experienced during the course of the disease and treatment are consistent with what has been reported in previous research (Chase and Wenzel, 2011; Fagotti et al., 2016; Sundar et al., 2022). Fatigue has been highlighted as one of the most common and impactful symptoms experienced by cancer patients, as it can profoundly affect a patients' ability to perform daily activities, engage in social activities, and maintain their mental and emotional well-being (Butt et al., 2008).

4.1.2. Health state utility

Utilities were elicited directly from patients by means of the EQ-5D-5L, a generic and cancer-specific validated preference-weighted instrument. Our study is unique among other reports of health state utilities associated with ovarian cancer treatment as many studies of health-technology assessment studies have relied on assumptions or consensus judgments of clinical experts rather than on patient-reported data (Bristow et al., 2007; Havrilesky et al., 2008; Lesnock et al., 2011; Forde et al., 2016; Uppal et al., 2012). One study reported health state descriptions from a small number of patients while receiving chemotherapy based on the EORTC QLQ-C30 questionnaire, but the corresponding utility estimates were provided by random members of the general public who were not representative of the target population in terms of socioeconomic status and ethnicity. The mean utility values ranged from 0.69 to 0.98 (Stein et al., 2007). Another study used the time trade-off method based on values reported by healthy volunteers, which does not accurately represent the target population of ovarian cancer patients. The reported mean utility at diagnosis was 0.55, which is lower compared to our data. In clinical remission, a mean utility of 0.83 was reported, which is similar to our results (Havrilesky et al., 2009). While several large clinical trials have collected preference-based measures of HRQoL in ovarian cancer patients, these trials address specific clinical questions, report utilities in limited health states and with short follow-up, and the populations may not always be representative of real-world patients. Nevertheless, we found mean utilities in a range similar to the utilities reported in these clinical trials (Friedlander et al., 2021; Mirza et al., 2016; van de Vrie et al., 2017).

4.2. Limitations

Our study has certain limitations. Most participants were Caucasian. Although the population showed good variation in most other demographic and clinical characteristics, there is the potential for nonresponse bias. This type of bias refers to the possibility that individuals who declined to participate in the study differ in some meaningful way from those who did participate, which may affect the generalizability of the results. Therefore, when interpreting the results, it is important to note that 18 % of the questionnaires were not returned. In this case, nonresponse may have been caused by factors such as treatment-related toxicity, physical status, (health) literacy and other sociodemographic characteristics. For example, the rate of highly educated participants in our study (41,5%) was slightly higher compared to the Dutch population (35,5 %, *Statistic Netherlands*). Another limitation of this study is its cross-sectional design. A longitudinal design would have been more appropriate to assess changes in HRQoL and utility over time. However, this type of study is often not feasible due to time constraints, workload, and patient burden. Finally, to increase the inclusion, patients were allowed to participate in more than one health state. This may have resulted in incomplete unpaired observations, meaning that some of the observations in one health state are not fully independent of another health state.

This study was partially conducted during the COVID-19 pandemic, which may have influenced the outcomes. There was a diagnostic delay, more frequent postponement or cancellation of outpatient clinic visits, and a reduction in non-urgent care (rehabilitation, psychological support) (van de Poll-Franse et al., 2021; Frey et al., 2020). These factors may have led to uncertainty, stress and depression (Frey et al., 2020). Studies have shown that the mental health of cancer patients during the COVID-19 pandemic was also affected by increased unemployment, physical distance, and lack of support networks (Islam et al., 2021; Wang et al., 2020). However, the impact of COVID-19 on mental well-being may have been greater in the general population than in cancer patients (van de Poll-Franse et al., 2021).

4.3. Implications for practice and future perspectives

This study contributes to the understanding of the impact of disease and treatment on HRQoL and health state utilities in a real-world ovarian cancer population. HRQoL and utilities were assessed using validated, well-established, and patient-centered methods. This represents a novel contribution to the existing literature on this topic. The health state utility data collected in this study can be used as a basis for calculating QALYs in future economic analyses, especially given the paucity of previously validated health state-related utilities.

An alternative approach to determining utilities involves the application of mapping techniques, which use statistical algorithms to convert available HRQoL data from non-preference measures into utility values (Longworth and Rowen, 2013). However, it is important to note that mapping is second best to direct measurement in patients due to the potential for loss of information and increased uncertainty. There are several mapping algorithms available that predict EQ-5D utility scores based on QLQ-C30 responses (Dakin et al., 2018). Prior to application, it is crucial to assess the validity of these algorithms for the target population to avoid bias. Currently, there are no algorithms specifically designed for the ovarian cancer population. The current dataset - with the combination of EORTC and EQ5D - allows the construction of a specific algorithm for ovarian cancer, providing the opportunity to use available HRQoL data in the absence of utility data for health economic evaluations.

The knowledge gained from this study can also be used in clinical practice to facilitate better treatment planning, informed decision-making, and individualized patient-centered care. The primary goals of ovarian cancer treatment should be to prolong both progression-free survival and overall survival, balanced with symptom relief and maintenance of patients' HRQoL. Continuous evaluation of the trade-offs between these domains is essential. These trade-offs become increasingly important in the palliative setting, where patients may undergo multiple cycles of chemotherapy or other therapies with cumulative side effects as potential benefits become less apparent. However, even in the first-line setting, it is understandable that frail patients may choose to decline CRS or chemotherapy, given the considerable impact on HRQoL. The final decision to continue or initiate a particular therapy should be based primarily on patient preferences, resulting in a balance between favorable treatment outcomes, patient goals and expectations, and patient attitudes toward (potential) complications, side effects, and impact on HRQoL.

PROMs have traditionally been used in clinical research and health technology assessment. However, their use in routine clinical practice is becoming more widespread, providing large population-based, longitudinal HRQoL and utility datasets that can be used to more accurately assess the impact of disease and treatment. The integration of PROMS into clinical practice also offers several clinical benefits, including improved physician-patient communication, enhanced decision-making, and early detection of treatment-related toxicities (Velikova et al., 2004). Furthermore, the collection of these data has the potential to extend treatment duration and even improve survival outcomes in certain contexts (Basch et al., 2016; Denis et al., 2017). The specific impact of routine HRQoL assessment on patients with advanced ovarian cancer has not yet been investigated.

4.4. Conclusion

This cross-sectional study assessed HRQoL and health state utilities in patients with advanced ovarian cancer using the validated EORTC QLQ-C30, QLQ-OV28, and EQ-5D-5L questionnaires. This study provides a useful and valuable resource for clinicians interested in understanding HRQoL and may aid in shared decision-making. Our data are highly relevant to research groups performing economic analyses, to guide policy development in advanced ovarian cancer. Ultimately, these combined HRQoL and utility data could form the basis of a mapping algorithm to convert HRQoL data from non-preference-based measures to health state utilities.

Financial support

No funding was received for the current study.

CRediT authorship contribution statement

Ruby M. van Stein: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Project administration. **Florine J. Hendriks:** Methodology, Investigation, Writing – review & editing. **Valesca P. Retèl:** Conceptualization, Methodology, Writing – review & editing. **Cor D. de Kroon:** Writing – review & editing, Supervision. **Christianne A.R. Lok:** Conceptualization, Writing – review & editing. **Gabe S. Sonke:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Kelly M. de Ligt:** Formal analysis, Methodology, Writing – review & editing, Supervision. **Willemien J. van Driel:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GS Sonke reports receiving institutional research support from Agendia, Biovica, AstraZeneca, Merck, Novartis, Roche and Seagen outside the scope of this study. The other authors have stated explicitly that there are no conflicts of interest in connection with this article.

References

Aaronson, N.K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N.J., et al., 1993. The european organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J. Natl Cancer Inst. 85 (5), 365–376.

Basch, E., Deal, A.M., Kris, M.G., Scher, H.I., Hudis, C.A., Sabbatini, P., et al., 2016. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. J. Clin. Oncol. 34 (6), 557–565.

Bristow, R.E., Santillan, A., Salani, R., Diaz-Montes, T.P., Giuntoli 2nd, R.L., Meisner, B. C., et al., 2007. Intraperitoneal cisplatin and paclitaxel versus intravenous carboplatin and paclitaxel chemotherapy for Stage III ovarian cancer: a cost-effectiveness analysis. Gynecol. Oncol. 106 (3), 476–481.

Butt, Z., Rosenbloom, S.K., Abernethy, A.P., Beaumont, J.L., Paul, D., Hampton, D., et al., 2008. Fatigue is the most important symptom for advanced cancer patients who have had chemotherapy. J. Natl. Compr. Canc. Netw. 6 (5), 448–455.

Chase, D.M., Wenzel, L., 2011. Health-related quality of life in ovarian cancer patients and its impact on clinical management. Expert Rev. Pharmacoecon. Outcomes Res. 11 (4), 421–431.

Dakin, H., Abel, L., Burns, R., Yang, Y., 2018. Review and critical appraisal of studies mapping from quality of life or clinical measures to EQ-5D: an online database and application of the MAPS statement. Health Qual. Life Outcomes 16 (1), 31.

Denis, F., Lethrosne, C., Pourel, N., Molinier, O., Pointreau, Y., Domont, J., et al., 2017. Randomized trial comparing a web-mediated follow-up with routine surveillance in lung cancer patients. J. Natl Cancer Inst. 109 (9).

Fagotti, A., Ferrandina, G., Vizzielli, G., Fanfani, F., Gallotta, V., Chiantera, V., et al., 2016. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): final analysis of peri-operative outcome. Eur. J. Cancer 59, 22–33.

Fayers PM, A.N., Bjordal, K., Groenvold, M., Curran, D., Bottomley, A., 2001. On behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual, 3rd ed. Published by: European Organisation for Research and Treatment of Cancer, Brussels.

Forde, G.K., Chang, J., Ziogas, A., 2016. Cost-effectiveness of primary debulking surgery when compared to neoadjuvant chemotherapy in the management of stage IIIC and IV epithelial ovarian cancer. Clinicoecon. Outcomes Res. 8, 397–406.

Frey, M.K., Ellis, A.E., Zeligs, K., Chapman-Davis, E., Thomas, C., Christos, P.J., et al., 2020. Impact of the coronavirus disease 2019 pandemic on the quality of life for women with ovarian cancer. Am. J. Obstet. Gynecol. 223(5):725.e1-.e9.

Friedlander, M., Moore, K.N., Colombo, N., Scambia, G., Kim, B.G., Oaknin, A., et al., 2021. Patient-centred outcomes and effect of disease progression on health status in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation receiving maintenance olaparib or placebo (SOLO1): a randomised, phase 3 trial. Lancet Oncol. 22 (5), 632–642.

Giesinger, J.M., Kieffer, J.M., Fayers, P.M., Groenvold, M., Petersen, M.A., Scott, N.W., et al., 2016. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. J. Clin. Epidemiol. 69, 79–88.

Giesinger, J.M., Loth, F.L.C., Aaronson, N.K., Arraras, J.I., Caocci, G., Efficace, F., et al., 2020. Thresholds for clinical importance were established to improve interpretation of the EORTC QLQ-C30 in clinical practice and research. J. Clin. Epidemiol. 118, 1–8.

Greimel, E., Bottomley, A., Cull, A., Waldenstrom, A.C., Arraras, J., Chauvenet, L., et al., 2003. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur. J. Cancer 39 (10), 1402–1408.

Havrilesky, L.J., Secord, A.A., Darcy, K.M., Armstrong, D.K., Kulasingam, S., 2008. Cost effectiveness of intraperitoneal compared with intravenous chemotherapy for women with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J. Clin. Oncol. 26 (25), 4144–4150.

Havrilesky, L.J., Broadwater, G., Davis, D.M., Nolte, K.C., Barnett, J.C., Myers, E.R., et al., 2009. Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. Gynecol. Oncol. 113 (2), 216–220.

Islam, J.Y., Vidot, D.C., Camacho-Rivera, M., 2021. Evaluating mental health-related symptoms among cancer survivors during the COVID-19 pandemic: an analysis of the COVID impact survey. JCO Oncol Pract. 17 (9), e1258–e1269.

Kehoe, S., Hook, J., Nankivell, M., Jayson, G.C., Kitchener, H., Lopes, T., et al., 2015. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet 386 (9990), 249–257.

Kim, J.H., Lee, D.E., Lee, Y., Ha, H.I., Chang, Y.J., Chang, S.J., et al., 2022. Quality of life outcomes from the randomized trial of hyperthermic intraperitoneal chemotherapy following cytoreductive surgery for primary ovarian cancer (KOV-HIPEC-01). J. Gynecol. Oncol. 33 (4), e54.

Koole, S.N., Kieffer, J.M., Sikorska, K., Schagen van Leeuwen, J.H., Schreuder, H.W.R., Hermans, R.H., et al., 2019. Health-related quality of life after interval cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with stage III ovarian cancer. Eur. J. Surg. Oncol.

Kumar, S., Long, J., Kehoe, S., Sundar, S., Cummins, C., 2019. Quality of life outcomes following surgery for advanced ovarian cancer: a systematic review and meta-analysis. Int. J. Gynecol. Cancer 29 (8), 1285–1291.

Lee, Y.C., King, M.T., O'Connell, R.L., Lanceley, A., Joly, F., Hilpert, F., et al., 2022. Symptom burden and quality of life with chemotherapy for recurrent ovarian cancer: the Gynecologic Cancer InterGroup-Symptom Benefit Study. Int. J. Gynecol. Cancer 32 (6), 761–768.

Lesnock, J.L., Farris, C., Krivak, T.C., Smith, K.J., Markman, M., 2011. Consolidation paclitaxel is more cost-effective than bevacizumab following upfront treatment of advanced epithelial ovarian cancer. Gynecol. Oncol. 122 (3), 473–478.

Longworth, L., Rowen, D., 2013. Mapping to obtain EQ-5D utility values for use in NICE health technology assessments. Value Health 16 (1), 202–210.

Mirza, M.R., Monk, B.J., Herrstedt, J., Oza, A.M., Mahner, S., Redondo, A., et al., 2016. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N. Engl. J. Med. 375 (22), 2154–2164.

Nolte, S., Liegl, G., Petersen, M.A., Aaronson, N.K., Costantini, A., Fayers, P.M., et al., 2019. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. Eur. J. Cancer 107, 153–163.

Reid, B.M., Permuth, J.B., Sellers, T.A., 2017. Epidemiology of ovarian cancer: a review. Cancer Biol. Med. 14 (1), 9–32.

Stein, K., Sugar, C., Velikova, G., Stark, D., 2007. Putting the 'Q' in quality adjusted life years (QALYs) for advanced ovarian cancer - an approach using data clustering methods and the internet. Eur. J. Cancer 43 (1), 104–113.

Sun, C.C., Ramirez, P.T., Bodurka, D.C., 2007. Quality of life for patients with epithelial ovarian cancer. Nat. Clin. Pract. Oncol. 4 (1), 18–29.

Sundar, S., Cummins, C., Kumar, S., Long, J., Arora, V., Balega, J., et al., 2022. Quality of life from cytoreductive surgery in advanced ovarian cancer: investigating the association between disease burden and surgical complexity in the international, prospective, SOCQER-2 cohort study. BJOG 129 (7), 1122–1132.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., et al., 2021. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 71 (3), 209–249.

Uppal, S., Hernandez, E., Dutta, M., Dandolu, V., Rose, S., Hartenbach, E., 2012. Prolonged postoperative venous thrombo-embolism prophylaxis is cost-effective in advanced ovarian cancer patients. Gynecol. Oncol. 127 (3), 631–637.

van de Poll-Franse, L.V., de Rooij, B.H., Horevoorts, N.J.E., May, A.M., Vink, G.R., Koopman, M., et al., 2021. Perceived care and well-being of patients with cancer and matched norm participants in the COVID-19 CRISIS: RESULTS OF A SURVEY OF PARTICIPANTS in the Dutch PROFILES registry. JAMA Oncol. 7 (2), 279–284.

van de Vrie, R., van Meurs, H.S., Rutten, M.J., Naaktgeboren, C.A., Opmeer, B.C., Gaarenstroom, K.N., et al., 2017. Cost-effectiveness of laparoscopy as diagnostic tool before primary cytoreductive surgery in ovarian cancer. Gynecol. Oncol. 146 (3), 449–456.

Velikova, G., Booth, L., Smith, A.B., Brown, P.M., Lynch, P., Brown, J.M., et al., 2004. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. J. Clin. Oncol. 22 (4), 714–724.

Versteegh, M., Vermeulen, K., Evers, S., de Wit, G., Prenger, R., Stolk, E., 2016. Dutch tariff for the five-level version of EQ-5D. Value Health 19 (4), 343–352.

Wang, Y., Duan, Z., Ma, Z., Mao, Y., Li, X., Wilson, A., et al., 2020. Epidemiology of mental health problems among patients with cancer during COVID-19 pandemic. Transl. Psychiatry 10 (1), 263.

Wilson, M.K., Friedlander, M.L., Joly, F., Oza, A.M., 2018. A Systematic review of health-related quality of life reporting in ovarian cancer phase III clinical trials: room to improve. Oncologist 23 (2), 203–213.

Wolowacz, S.E., Briggs, A., Belozeroff, V., Clarke, P., Doward, L., Goeree, R., et al., 2016. Estimating health-state utility for economic models in clinical studies: an ISPOR good research practices task force report. Value Health 19 (6), 704–719.