ACTA ONCOLOGICA
2019, VOL. 58, NO. 5, 790–800
https://doi.org/10.1080/0284186X.2018.1560498

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ORIGINAL ARTICLE

Changes in health-related quality of life among gynecologic cancer survivors during the two years after initial treatment: a longitudinal analysis

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ABSTRACT

Background: While many cancer survivors experience persistent impairments in health-related quality of life (HRQoL) for extended periods of time, others recover soon after treatment. The aim of this research is to assess changes in health-related quality of life in endometrial and ovarian cancer survivors during two years post initial treatment, and to assess clinical and sociodemographic characteristics associated with those changes.

Methods: This prospective population-based cohort study includes longitudinal data of endometrial ($N = 221$) and ovarian ($N = 174$) cancer survivors diagnosed between 2011 and 2014. The EORTC QLQ-C30 functioning scales were used to assess HRQoL after initial treatment and after 6, 12 and 24 months. Clinical (stage, treatment and comorbidities) and sociodemographic (age, marital status and socio-economic status) characteristics were obtained from the Netherlands Cancer Registry and through self-administered questionnaires. Linear mixed models were used to assess changes in HRQoL over time and characteristics associated with these changes.

Results: Among both endometrial and ovarian cancer patients, HRQoL improved within the first 6 months after initial treatment. Changes in HRQoL were mainly associated with clinical characteristics including comorbidities, treatment and tumor stage, and to a lesser extent with sociodemographic characteristics such as socioeconomic status. However, these associations varied per tumor type. Endometrial cancer survivors, who received radiotherapy and had no comorbidities, reported greater improvements in some HRQoL scales over time. Ovarian cancer patients who received chemotherapy and with advanced tumor stages reported poorer functioning during treatment. Most functioning domains (global health, physical and role functioning) recovered to levels of patients without chemotherapy or with early-stage disease after 12 months, but cognitive and social functioning remained impaired.

Conclusion: Some subgroups of patients, including those with multiple comorbidities, with an advanced tumor stage and who received chemotherapy, may be in need of additional support as they are less likely to show improvements in HRQoL over time.

ARTICLE HISTORY
Received 21 August 2018
Accepted 10 December 2018

Introduction

Due to the aging population, earlier diagnosis and improved treatments, the worldwide population of gynecological cancer survivors has been growing in the past decades [1]. The two most common gynecological cancer types are endometrial and ovarian cancer, accounting worldwide for 9 percent of the cancer incidence among women in 2012 [2]. In the Netherlands, the number of women living with or after endometrial or ovarian cancer increased from 15,540 in the year 2000 to 18,671 in 2015 [3].

Women with endometrial or ovarian cancer frequently struggle with physical and psychosocial problems, including pain, fatigue, anxiety, distress and depression, resulting in a decreased health-related quality of life (HRQoL) [4]. HRQoL is a measure of the daily functioning of a cancer survivor and varies considerably between cancer survivors and over time depending on clinical and sociodemographic characteristics [5]. Characteristics associated with HRQoL have mostly been evaluated in cross-sectional studies [6–9] which included small and selective samples [6] or did not cover a broad range of HRQoL outcomes [10]. Other studies evaluated HRQoL as part of a clinical trial, with selective samples [8,11]. As evaluated in clinical trials, a poorer HRQoL has been found in patients with a higher tumor stage [12] and in

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patients receiving radiotherapy or chemotherapy compared to patients without adjuvant therapy [8,11]. Furthermore, cross-sectional studies found that comorbidity [7], lower socioeconomic status (SES) [13] and not having a partner [6,9] were associated with a poorer HRQoL. Other cross-sectional studies found that younger age was associated with poorer global health and emotional functioning, while older patients showed poorer physical functioning [6,7,10].

Associations of clinical and sociodemographic characteristics with the changes in HRQoL after treatment, however, remain unclear. Knowledge about characteristics associated with these changes could provide insight into why some patients are more resilient and recover soon after treatment, while others experience persistent impairments in HRQoL and may need additional support to improve their HRQoL. This may guide the future development of patient-tailored care.

The aim of this study is to assess changes in HRQoL in a population-based sample of endometrial and ovarian cancer survivors during two years post initial treatment, and to assess clinical and sociodemographic characteristics associated with those changes. It is hypothesized that for both endometrial and ovarian cancer a decline of the HRQoL is observed after initial treatment, and that the HRQoL improves after completion of initial treatment. We expect that patients that are younger, single, have a lower SES, received radiotherapy or chemotherapy, have more comorbidities, and a higher tumor stage after initial treatment are at risk of maintaining an impaired HRQoL in the two years following initial treatment.

Methods

Design

For this study, the data of the Registration system Oncological GYnecology (ROGY) Care trial has been analyzed as a prospective cohort study with a two-year follow-up. In this longitudinal cluster randomized controlled clinical trial (RCT), 12 hospitals were pre-randomized to either providing patients with a 'Survivorship Care Plan' (SCP) or providing care as usual. Patients in the 'SCP care' arm received a document which stated patient characteristics such as disease characteristics, the treatments the patient received, the effects of the treatments and information concerning supportive care services [14]. Previously, it has been shown that the intervention did not have a direct effect on HRQoL [14], allowing us to use the data as a cohort study to answer our research question. The ROGY Care trial has been approved by the medical research ethics committees of all participating centers [14].

Population

Women who were diagnosed with endometrial cancer between April 2011 and October 2012 or with ovarian cancer between April 2011 and March 2014 in the 12 participating hospitals were invited to participate. The inclusion period of ovarian cancer patients was longer due to the lower incidence of the disease and due to one hospital not including ovarian cancer patients. After initial treatment, the patients received a letter and a leaflet to inform them about the study and an informed consent form from their gynecologist. Participants were asked to complete follow-up questionnaires after 6, 12 and 24 months. At the time point 'after initial treatment' patients completed surgery but could still be receiving radiotherapy or chemotherapy. Treatment regiments were stable during the inclusion period [15]. Patients were not aware that they participated in an intervention trial on SCPs.

Participants with all tumor stages were included if they were 18 years and older, and able to fill out a Dutch questionnaire. Patients diagnosed with borderline ovarian cancer, and under palliative care were excluded [14]. In total, 544 women fulfilled the inclusion criteria, of which 296 women had endometrial cancer and 248 had ovarian cancer. In the current analysis data of patients with progressive or recurrent cancer were excluded. More specifically, patients with progressive cancer who did not receive curative treatment were excluded and follow-up data were excluded if a patient was diagnosed with recurrent cancer before or within a month after completion of the follow-up questionnaire. Disease status was obtained from the medical files at the end of the study. Data from the twelve patients that died during the follow-up period from a cause other than disease progression or recurrence were excluded from 6 months prior to death, because their HRQoL may be affected in that period [16]. Patients with an unknown date of the diagnosis of recurrence and patients with missing data on all HRQoL scales at baseline were excluded as well.

The first questionnaire was returned by 221 endometrial (75%) and 174 ovarian cancer patients (70%). Follow-up questionnaires were completed after 6 months (endometrium $n = 158$ [53%]; ovarium $n = 124$ [50%]), 12 months (endometrium $n = 147$ [50%]; ovarium $n = 101$ [41%]) and 24 months (endometrium $n = 128$ [43%]; ovarium $n = 75$ [30%]) (Figure 1).

Measurements

Health-related quality of life

HRQoL was measured using the European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30) [17]. The QLQ-C30 includes five functioning scales (cognitive, role, physical, emotional and social) and a global health/QoL scale. The 15 items regarding the functioning scales were answered on a 4-point scale with the following anchors: 'not at all', 'a little', 'quite a bit' and 'very much'. The two items of the global health/QoL scale have a 7-point answering scale ranging from very poor to excellent. Scores for each scale were linear transformed into a 0–100 outcome. A higher score indicates a higher functioning or global health/QoL. The QLQ-C30 is known to be a reliable measure with test-retest reliability coefficients ranging from 0.63 to 0.91 on the different functioning scales [17]. The internal constancy of the scales in our population was good (Cronbach's alpha 0.83–0.86).

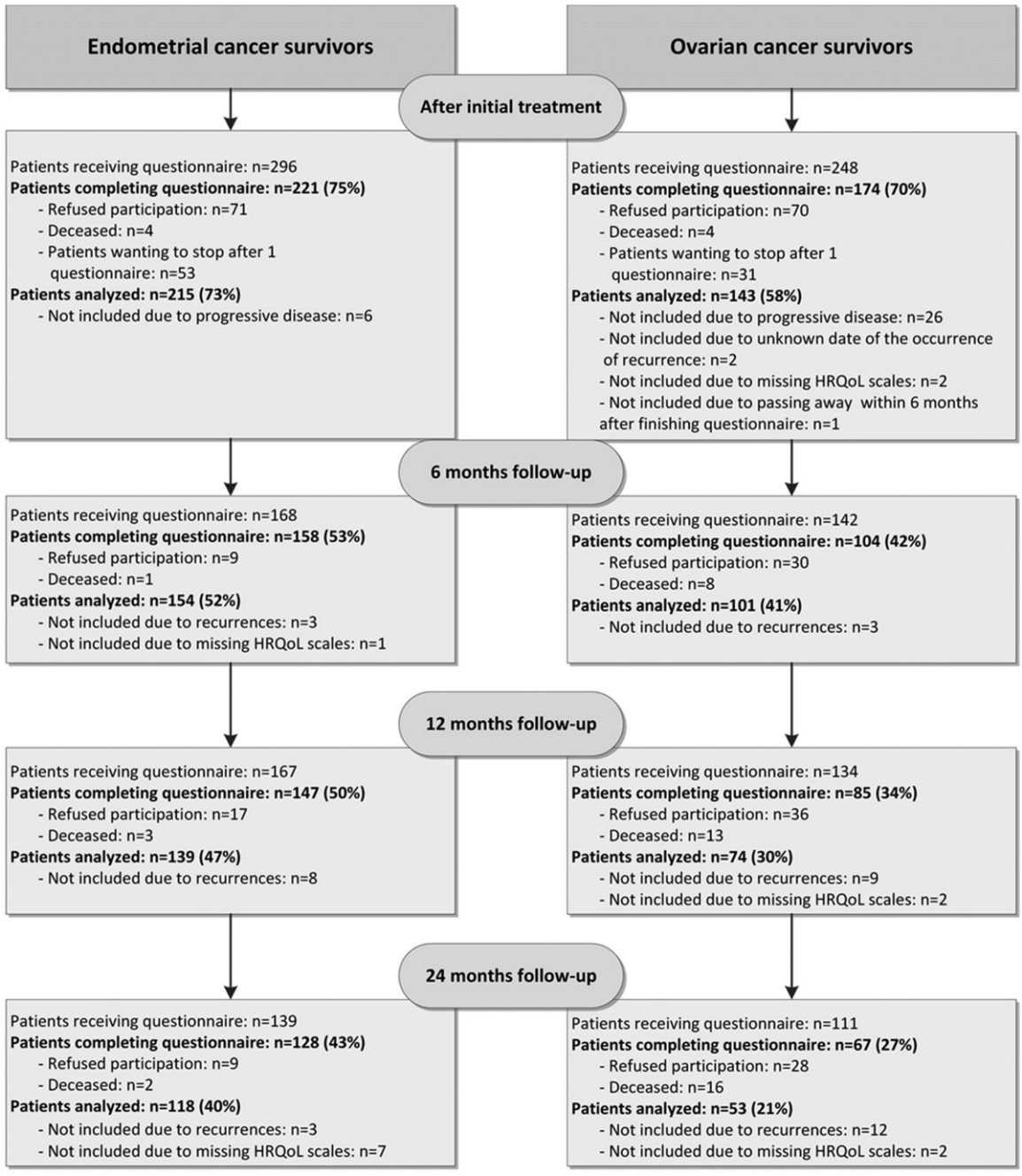

Figure 1. Flowchart of the inclusion and follow-up in the ROGY care trial for both endometrial and ovarian cancer survivors.

Clinical and sociodemographic characteristics

Clinical (treatment and tumor stage) and sociodemographic (age [continuous] and SES) characteristics, were obtained from the Netherlands Cancer Registry (NCR). The tumor stage is based on the International Federation of Gynecology and Obstetrics (FIGO) [18,19]. For the analyses, FIGO stage was dichotomized into early (stage I) and advanced (stage II/III/IV) stage. Treatment was coded as either receiving the treatment or not (surgery [yes/no], chemotherapy [yes/no] and radiotherapy [yes/no]). SES (categorized: low/intermediate/high) is based on the postal code of the residential area of the patient, by combining the mean household income and the mean value of housing, derived from aggravated individual fiscal data [20]. SES was measured in 4 categories low, intermediate, high and institutionalized/unknown, by which the latter category was reported as missing. Comorbidities (categorized: no comorbidities/one comorbidity/two or more comorbidities) [21] and marital status (dichotomized: partner [married or living together]/no partner[divorced, widowed or never married]) were measured using the self-administered questionnaires.

Statistical analyses

Descriptive statistics

Patient characteristics were evaluated by using descriptive statistics, stratified by cancer type. Dichotomous and categorical characteristics were described with frequencies (n) and percentages (%) and continuous characteristics were

described with means (M) and standard deviations (SD) if normally distributed and with medians and quartiles (25th–75th) if not normally distributed. Continuous variables were checked for normal distribution and for homogeneity of the variances. Differences between full responders (completing all four questionnaires) and responders who filled out one to three questionnaires (lost to follow-up) were examined by X^2-tests for categorical variables and by independent sample *t*-tests for continuous variables with a normal distribution. Statistical Analysis System (SAS) version 9.4. (SAS Institute, Cary, NC, 1999) was used to conduct the statistical analyses.

Longitudinal linear mixed model analyses

Longitudinal linear mixed model analyses were performed to assess the changes in HRQoL over time for all five functional scales and the global health/QoL scale. These continuous dependent variables were analyzed with time as an independent categorical variable (after initial treatment and at 6, 12 and 24 months). Using time as a categorical variable is allowed since all patients are measured at the same time points [22]. A random intercept for the patient was included to correct for dependency of the repeated observation within the patients. A random intercept for the hospital to adjust for clustering on hospital level was not needed (ICC: 0–0.05). Longitudinal linear mixed model analysis corrects for data missing at random [22].

Additionally, sensitivity analysis of the longitudinal linear mixed model analyses was performed, only including individuals that completed all four questionnaires (full responders). Findings that changed from non-significant to significant ($p < .05$) or vice versa were reported.

In the second step of the longitudinal linear mixed model analysis, all pre-defined confounders were added to the models simultaneously. Interaction terms were added to the models to assess whether characteristics had different effects on HRQoL at different points in time. The interaction 'time (as a categorical variable)×characteristic' was included and for each characteristic, a new model was calculated. The analyses were performed for both endometrial - and ovarian cancer patients separately; the sample sizes of both groups were sufficient to allow nine independent variables in a model [22]. All the baseline variables were taken into the model as time-independent variables [6,7,11,13]. Mixed model analysis handles missing data by using the known values to correct and estimate the unknown values [22], assuming that data is missing at random (MAR). For all the analyses the crude and adjusted model were presented, including the unstandardized beta-coefficients, the 95% confidence intervals and *p* values. Bonferroni correction is used to correct for multiple testing ($\alpha < 0.0083$). Clinical relevant differences of the HRQoL subscales is based on the 'Guidelines for interpretation of longitudinal QOL differences' of Cocks et al. [23] to either a trivial, small or medium clinical effect size (CES). The *p* values were considered statistically significant if $p < .05$ for associations and $p < .10$ for the interaction effects [22]. In case of significant moderation, stratified analyses showed HRQoL across the time points for each level of the moderator variable using graphs.

Results

Endometrial cancer patients who completed all questionnaires were on average younger than the patients who did not (65 years vs. 69 years; $p < .01$), they more often had a partner (84% vs. 66%; $p = .01$) and suffered less from multiple comorbidities (None: 25% vs. 13%, one: 29% vs. 22%, 2 or more: 45% vs. 62%; $p = .03$) (Table 1). Full responders within the group of ovarian cancer patients were younger in comparison to the non-full responders (61 years vs. 65 years; $p = .05$) and were less likely to have received chemotherapy (62% vs. 80%; $p = .02$).

Endometrial cancer patients

Table 2 summarizes the changes in HRQoL during follow-up (6, 12, and 24 months after treatment). A significant improvement in HRQoL was observed after six months for all scales except for cognitive functioning, which remained stable. Thereafter, most of the patients' HRQoL scales stabilized for all scales except for role and physical functioning, which showed a significant decrease after 12 months.

Table 3 shows the associations between clinical and sociodemographic characteristics and the HRQoL subscales during two years post initial treatment. Overall, patients with more than one comorbidity reported 9.0–13.4 points lower on all HRQoL scales. Patients with one comorbidity had a lower score on physical functioning in comparison with patients without comorbidities (−5.7 [10.0;−1.4]). Patients with advanced tumor stage had a worse global health (−7.0 [−13.5;−0.5]) and social functioning (9.7 [−17.7;−1.6]) than patients with early-stage disease. Higher age was associated with increased social functioning (0.4 [0.03;0.7]).

Furthermore, significant interactions ($p < .10$) with time were found for treatment on emotional functioning ($p = .06$) and cognitive functioning ($p = .02$), for SES on emotional functioning ($p = .02$), for comorbidities on physical functioning ($p < .01$). Endometrial cancer patients who received radiotherapy improved in their emotional and cognitive functioning over time, whereas those without radiotherapy stayed rather stable (Figure 2). However, this interaction effect was not significant in sensitivity analysis that only included full responders. Patients who had a high SES reported better emotional functioning than those with intermediate SES, especially early during follow-up, but this interaction effect was not significant in sensitivity analysis that only included full responders. Finally, patients with more comorbidities sharply decreased in their physical functioning over time, whereas those without comorbidities stayed rather stable.

Table 1. Clinical and sociodemographic characteristics of endometrial and ovarian cancer patients at baseline; the total population, and the full responders versus responders lost to follow-up.

	Endometrial cancer patients				Ovarian cancer patients			
	Total ($N = 215$)	Full Responder ($N = 69$)	Lost to follow-up ($N = 146$)	p value	Total ($N = 143$)	Full Responder ($N = 50$)	Lost to follow-up ($N = 93$)	p value
Age at initial treatment				**<.01**				**.05**
Mean (SD)	68.0 (9.0)	65.4 (7.5)	69.2 (9.4)		63.4 (10.9)	61.0 (9.2)	64.7 (11.6)	
SES, *N*(%)				.07				.35
High	78 (36)	32 (46)	46 (32)		52 (36)	19 (38)	33 (35)	
Intermediate	88 (41)	26 (38)	62 (42)		51 (36)	17 (34)	34 (37)	
Low	42 (20)	9 (13)	33 (23)		24 (17)	12 (24)	12 (13)	
Unknown	7 (3)	2 (3)	5 (3)		16 (11)	2 (4)	14 (15)	
Marital Status, *N*(%)				**.01**				.47
Partner	155 (72)	58 (84)	97 (66)		101 (71)	38 (76)	63 (68)	
No Partner	57 (27)	11 (16)	46 (32)		39 (27)	12 (24)	27 (29)	
Unknown	3 (1)	0 (0)	3 (2)		3 (2)	0 (0)	3 (3)	
Comorbidity, *N*(%)				**.02**				.55
No comorbidities	36 (17)	17 (25)	19 (13)		45 (31)	18 (36)	27 (29)	
1 comorbidity	55 (26)	22 (32)	33 (23)		45 (31)	16 (32)	29 (31)	
2 or more comorbidities	118 (55)	29 (42)	89 (61)		52 (36)	15 (30)	37 (40)	
Unknown	6 (3)	1 (1)	5 (3)		1 (1)	1 (2)	0 (0)	
Tumor stage, *N*(%)				.16				.09
Stage I	189 (88)	66 (96)	123 (84)		42 (29)	21 (42)	21 (23)	
Stage II	7 (3)	1 (1)	6 (4)		23 (16)	9 (18)	14 (15)	
Stage III	12 (6)	1 (1)	11 (8)		58 (41)	16 (32)	42 (45)	
Stage IV	5 (2)	1 (1)	4 (3)		16 (11)	4 (8)	12 (13)	
Unknown	2 (1)	0 (0)	2 (1)		4 (3)	0 (0)	4 (4)	
Primary Treatment, *N*(%)								
Surgery	213 (99)	69 (100)	144 (99)	.49	141 (99)	50 (100)	91 (98)	.30
Radiotherapy	74 (34)	23 (33)	51 (35)	.79	0 (0)	0 (0)	0 (0)	
Chemotherapy	11 (5)	0 (0)	11 (8)	**.02**	105 (73)	31 (62)	74 (80)	**.02**

Lost to follow-up: patients who did not complete at least one of the questionnaires at some point in time.
N: number of patients; SD: Standard Deviation; SES: Socioeconomic status. Significant p values ($p < .05$) are shown in bold.

Ovarian cancer patients

Ovarian cancer patients reported a significant increase in the first 6 months in all functioning scales except for cognitive functioning (Table 2). However, in sensitivity analysis of adjusted models that only included full responders, CF improved after 12 months (5.4 [0.3;10.5], $p = .04$) (not tabulated).

After 6 months the HRQoL stabilized on all functioning. Overall, patients without a partner had poorer HRQoL scores on most scales ranging from 8.0 to 13.6 points lower than those with a partner, except for emotional functioning (Table 3). Similarly, having multiple comorbidities was associated with poorer scores in most scales with 6.5–10.7 points lower, except for social functioning. Patients with a higher SES had a lower social functioning (−11.2 [−20.7;−1.7]) in comparison with patients with a low SES and a higher age was associated with an increase in cognitive functioning (0.5 [0.1;0.8]) and a decrease in physical functioning (−0.3 [−0.5;−0.006]).

Significant interactions of time with chemotherapy with nearly all HRQoL scores were found (global health/QoL, $p = .03$; social functioning, $p = .07$; cognitive functioning, $p = .04$, role functioning, $p = .02$, physical functioning, $p = .02$), and with tumor stage on role functioning ($p = .02$) and physical functioning ($p = .01$). Patients receiving chemotherapy improved more on global health/QoL, social, role and physical functioning than patients who did not receive chemotherapy. However, the scores overall remained lower for the patients after chemotherapy (Figure 2). Cognitive functioning remained stable for patients after chemotherapy, while improvements were seen in patients who did not receive chemotherapy. Patients with advanced tumor stage increased in the role and physical functioning over time, while patients with early-stage cancer increased less and stabilized.

Discussion

Among both endometrial and ovarian cancer patients, HRQoL substantially improved within the first 6 months after initial treatment. Changes in HRQoL were mainly associated with clinical characteristics including comorbidities, treatment and tumor stage, and to a lesser extent with sociodemographic characteristics such as SES. However, these associations varied per tumor type.

As hypothesized, among endometrial cancer patients, emotional, social and role functioning improved within 6 months after initial treatment. Surprisingly, at 12 and 18 months role and physical functioning worsened

Table 2. Changes in HRQoL during 2-years follow-up after initial treatment (reference) in multilevel linear regression analysis for both endometrial and ovarian cancer patients.

	Endometrial cancer patients						Ovarian cancer patients					
		Crude model		Adjusted model				Crude model		Adjusted model		
	Means	B	95%CI	B	95%CI	CES	Means	B	95%CI	B	95%CI	CES
Global health/QoL												
After initial treatment	74.3						65.1					
After 6 months	76.6	2.3	(−0.4;5.1)	3.0*	(0.23;5.8)	Tr	77.9	**12.0****	**(8.6;15.4)**	**11.4****	**(7.7;15.0)**	Me
After 12 months	77.2	2.5	(−0.4;5.3)	2.8	(−0.2;5.7)	Tr	77.9	**11.7****	**(7.8;15.5)**	**10.4****	**(6.3;15.0)**	Me
After 24 months	76.7	1.9	(−1.1;4.9)	2.4	(−0.7;5.5)	Tr	78.1	**11.2****	**(6.9;15.5)**	**9.5****	**(5.0;13.9)**	Me
Emotional functioning												
After initial treatment	81.0						77.3					
After 6 months	84.4	**4.3****	**(1.7;6.9)**	4.0**	**(1.3;6.8)**	Tr	83.9	**6.2****	**(2.4;10.0)**	**5.2****	**(1.1;9.2)**	Tr
After 12 months	83.9	**4.1****	**(1.4;6.8)**	**4.1****	**(1.3;6.9)**	Tr	78.4	−0.4	(−4.7;3.8)	−1.1	(−5.6;3.4)	Tr
After 24 months	84.6	**4.1****	**(1.2;6.9)**	3.8*	(0.8;6.8)	Tr	82.9	3.7	(−1.1;8.6)	2.4	(−2.6;7.3)	Tr
Social functioning												
After initial treatment	82.6						72.0					
After 6 months	88.1	**6.4****	**(3.1;9.7)**	**6.8****	**(3.3;10.3)**	Sm	81.3	**9.3****	**(4.9;13.7)**	**9.0****	**(4.2;13.8)**	Me
After 12 months	86.5	**5.0****	**(1.5;8.4)**	4.7*	(1.1;8.3)	Sm	87.2	**14.0****	**(9.0;18.9)**	**13.9****	**(8.7;19.2)**	Me
After 24 months	86.2	4.8*	(1.1;8.4)	**5.1****	**(1.3;9.0)**	Sm	88.1	**13.6****	**(8.0;19.2)**	**12.8****	**(7.0;18.6)**	Me
Cognitive functioning												
After initial treatment	84.5						78.6					
After 6 months	86.4	2.3	(−0.4;5.0)	2.2	(−0.7;5.1)	Tr	80.2	1.3	(−2.4;5.0)	0.1	(−3.9;4.2)	Tr
After 12 months	85.6	1.9	(−0.9;4.7)	2.1	(−0.9;5.1)	Tr	81.8	3.4	(−0.8;7.5)	2.8	(−1.7;7.3)	Tr
After 24 months	86.4	2.2	(−0.8;5.2)	1.6	(−1.7;4.7)	Tr	81.4	2.9	(−1.9;7.6)	2.3	(−2.7;7.3)	Tr
Role functioning												
After initial treatment	84.1						57.4					
After 6 months	88.0	4.7*	(0.9;8.4)	5.0*	(0.9;9.0)	Tr	73.7	**16.1****	**(10.7;21.6)**	**15.2****	**(9.4;21.2)**	Me
After 12 months	89.2	**5.7****	**(1.8;9.6)**	**5.8****	**(1.6;10.0)**	Tr	79.7	**21.2****	**(15.1;27.3)**	**20.2****	**(13.7;26.8)**	Me
After 24 months	76.4	**−5.8****	**(−9.8;1.8)**	**−6.5****	**(−10.8;−2.2)**	Tr	82.7	**23.5****	**(16.6;30.4)**	**21.1****	**(14.0;28.3)**	Me
Physical functioning												
After initial treatment	90.0						70.3					
After 6 months	91.7	2.3*	(0.3;4.4)	2.7*	(0.5;4.9)	Sm	79.4	**9.0****	**(5.5;12.4)**	**8.1****	**(4.5;11.8)**	Me
After 12 months	92.4	2.1	(−0.1;4.2)	2.4*	(0.1;4.7)	Sm	80.0	**8.2****	**(4.3;12.0)**	**7.7****	**(3.6;11.7)**	Me
After 24 months	77.1	**−10.3****	**(−12.4;−8.1)**	**−10.5****	**(−12.8;−8.1)**	Me	82.9	**10.4****	**(6.0;14.8)**	**8.8****	**(4.3;13.3)**	Me

*$p < .05$ and **$p < .0083$ (Bonferroni correction), p values $<.0083$ are shown in bold. Analyses were, adjusted for age, SES, marital status, comorbidities, tumor stage, radiotherapy for endometrial cancer patients, and chemotherapy for ovarian cancer patients. HRQoL subscales ranged from 0 to 100. CES: clinical effect size; Tr: trivial; Sm: small; Me: medium.

dramatically. Deteriorations in physical functioning were partly explained by comorbidities at baseline. Furthermore, endometrial cancer patients that received radiotherapy improved in emotional and cognitive functioning, while those with comorbidities decreased in physical functioning.

Similarly, among ovarian cancer patients we found improvements in emotional, role and physical functioning and global health after 6 months, however, improvements in emotional functioning did not persist. Those who received chemotherapy and had advanced stage disease had a lower HRQoL at the start of the study, but improved over time. Global health/QoL, physical and role functioning even improved to levels equivalent to those with early staged disease and those without receiving chemotherapy, while cognitive and social impairments remained worse compared to those without receiving chemotherapy. Our sensitivity analyses showed that almost all results remain similar when only including patients that completed all questionnaires, suggesting that there is no substantial bias of selective lost to follow-up.

Endometrial cancer patients

Similar to our findings, previous studies have also reported improvements in HRQoL within 6–12 months to levels equivalent to other cancer populations and the general population [8,24]. Further, deteriorations of the role and physical functioning after one year were in line with findings from the PORTEC-1 trial from Nout et al. [8], in which patients were randomized to either receiving or not receiving radiotherapy. Side effects of radiotherapy may have been the cause of the poorer HRQoL subscales. Radiotherapy can cause long-term diarrhea, bowel and urinal incontinence even 15 years post-treatment. On the contrary, we did not observe worse role- and physical functioning among patients receiving adjuvant radiotherapy. Instead, we found that endometrial cancer patients who received radiotherapy compared to surgery only showed greater improvements in emotional and cognitive functioning resulting in a higher HRQoL at 12 and 24 months. However, these findings may be biased because relatively many patients who received radiotherapy were lost-to-follow-up due to death or ill-health, resulting in a selective subgroup of healthier patients as observed after 12 and 24 months.

Previous literature has shown mixed results, some studies reported higher HRQoL after surgery and adjuvant radiotherapy and others have shown that surgery only is associated with a higher HRQoL [11]. In addition, patients with a low and intermediate SES reported improved emotional functioning over time, while patients with a high SES reported a higher but stable emotional functioning. This is in line with the literature where a low SES is associated with a poorer HRQoL [6]. Patients with one or multiple comorbidities experienced a decline in physical functioning after 12 months,

Table 3. Associations between socio-demographic and clinical characteristics and HRQoL scales during 2-years follow-up after initial treatment in multilevel multivariable linear regression analysis.

	B (95% CI)											
	Global health/QoL		Emotional functioning		Social functioning		Cognitive functioning		Physical functioning		Role functioning	
Endometrial cancer patients												
Age	0.1	(−0.1;0.4)	0.3	(−0.03;0.5)	0.4*	(0.03;0.7)	0.1	(−0.2;0.4)	−0.1	(−0.3;0.1)	0.01	(−0.3;0.3)
SES (ref: Low)												
Intermediate	2.2	(−3.6;8.0)	−2.5	(−8.9;3.9)	−6.2	(−13.4;1.1)	−1.4	(−8.2;5.4)	−1.9	(−5.8;2.1)	−4.3	(−10.6;2.0)
High	3.8	(−2.2;9.7)	1.9	(−4.7;3.9)	−4.4	(−11.8;3.0)	−1.6	(−8.6;5.4)	−2.0	(−6.0;2.1)	−2.1	(−8.4;4.2)
Marital Status (ref: Partner)												
No partner	−3.4	(−8.5;1.8)	−2.7	(−8.4;3.0)	−5.9	(−12.3;0.6)	−0.8	(−6.8;5.3)	−0.03	(−3.5;3.5)	1.3	(−4.2;6.8)
Comorbidity (ref: none)												
One	−4.3	(−10.9;2.3)	−1.6	(−8.9;5.7)	−6.1	(−14.2;2.1)	−4.6	(−12.3;3.1)	**−5.7****	**(−10.0;−1.4)**	−1.3	(−8.1;5.4)
Two or more	**−13.4****	**(−19.2 ; −7.7)**	**−9.0****	**(−15.3;−2.6)**	**−10.2****	**(−17.4;−3.1)**	**−11.2****	**(−17.9;−4.5)**	**−10.2****	**(−13.9;−6.4)**	**−9.7****	**(−15.5 ;−3.9)**
Tumor Stage (ref: stage I)												
Stage II/III/IV	−7.0*	(−13.5;−0.5)	−4.9	(−12.0;2.3)	−9.7*	(−17.7;−1.6)	0.4	(−7.1;7.9)	−2.0	(−6.4;2.4)	−0.5	(−7.9;6.9)
Treatment												
Radiotherapy (yes vs. no(ref))	2.4	(−2.3;7.0)	2.8	(−2.4;7.9)	1.8	(−4.0;7.5)	2.9	(−2.5;8.4)	1.1	(−2.1;4.2)	1.6	(−3.3;6.4)
Ovarian cancer patients												
Age	0.1	(−0.2;0.3)	0.2	(−0.1;0.5)	0.2	(−0.2;0.5)	0.5*	(0.1;0.8)	−0.3*	(−0.5;−0.006)	0.2	(−0.1;0.6)
SES (ref: Low)												
Intermediate	−2.4	(−9.6;4.8)	−4.2	(−12.9;4.6)	−5.9	(−15.4;3.6)	−4.0	(−13.8;5.8)	0.7	(−6.7;8.0)	−5.1	(−15.6;5.3)
High	−4.2	(−11.3;3.0)	−4.0	(−12.7;4.7)	−11.2*	(−20.7;−1.7)	−3.9	(−13.6;5.9)	2.2	(−5.1;9.5)	−6.1	(−16.4;4.3)
Marital Status (ref: Partner)												
No partner	**−10.5****	**(−16.3;−4.7)**	−2.8	(−9.9;4.3)	**−13.6****	**(−21.3;−5.8)**	−7.9	(−15.9;0.01)	**−10.5****	**(−16.5;−4.5)**	**−13.7****	**(−22.2;−5.3)**
Comorbidity (ref: none)												
One	2.5	(−3.7;8.8)	−1.5	(−9.1;6.2)	−7.1	(−15.4;1.2)	−8.2	(−16.8;0.4)	2.8	(−3.6;9.1)	−2.5	(−11.5;6.6)
Two or more	−7.7*	(−1.0;−1.4)	−8.1*	(−15.8;−0.3)	−4.5	(12.9;3.9)	−10.4*	(−19.1;−1.7)	−6.6*	(−13.1;−0.1)	−11.0*	(−20.2;−1.9)
Tumor Stage (ref: stage I)												
Stage II/III/IV	−0.9	(−10.9;9.2)	−7.4	(−19.6;4.8)	−1.9	(−15.2;11.4)	−10.6	(−24.3;3.1)	−1.4	(−11.6;8.8)	−1.0	(−15.5;13.5)
Treatment												
Chemotherapy (yes vs. no(ref))	−5.3	(−15.6;5.0)	11.1	(−1.5;23.6)	−5.4	(−19.0;8.2)	4.5	(−9.5;18.5)	−5.7	(−16.2;4.8)	−10.8	(−25.7;4.2)

*$p < .05$ and **$p < .0083$ (Bonferroni correction), p values $<.0083$ are shown in bold. Analyses were, adjusted for age, SES, marital status, comorbidities, tumor stage, radiotherapy for endometrial cancer survivors, and chemotherapy for ovarian cancer survivor. HRQoL subscales ranged from 0 to 100.

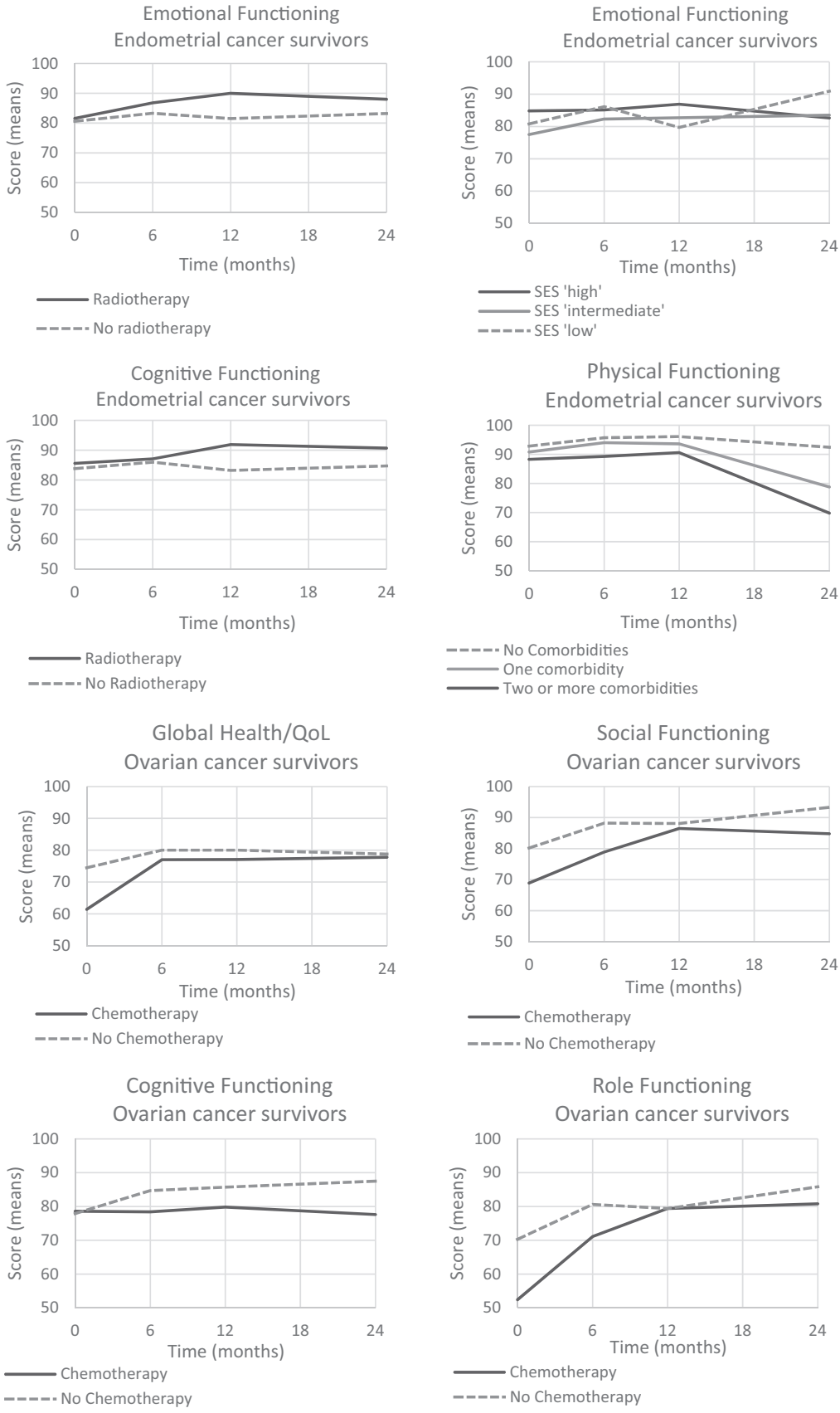

Figure 2. Stratified analyses showing mean scores of HRQoL over time by level of the moderator variable for those characteristics where the interaction term was significant and thus where HRQoL differed between the levels of the moderator variable. Analyses were, adjusted for age, SES, marital status, comorbidities, tumor stage, radiotherapy for endometrial cancer patients and chemotherapy for ovarian cancer patients.

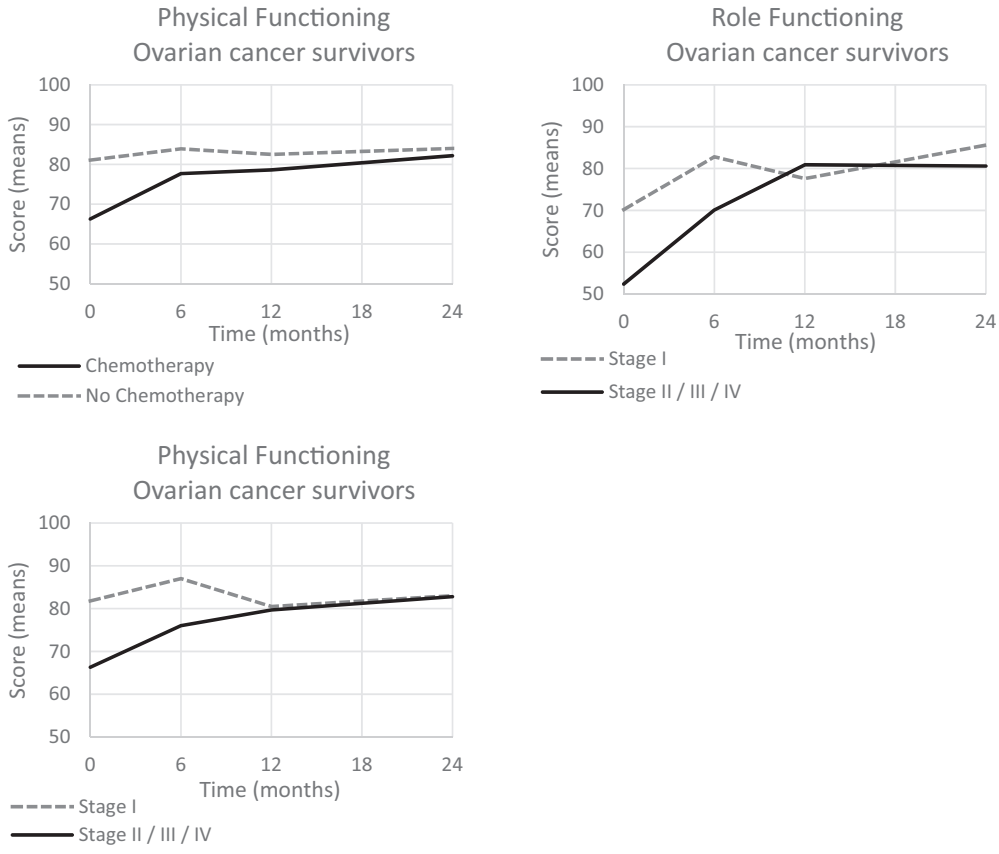

Figure 2. (Continued)

while patients with no comorbidities had a stable physical functioning. This suggests that comorbidities at baseline may explain impairments in physical functioning over time. Unfortunately, numbers in our analysis were too small to assess which comorbidities had the largest impact on physical functioning, but the literature suggests that obesity, diabetes and cardiovascular disease may play an important role [11].

Ovarian cancer patients

The improvements in most HRQoL functioning scales among ovarian cancer patients in our sample is in line with the literature [8,24]. As expected, ovarian cancer patients who received chemotherapy and those with advanced tumor stages, reported poorer functioning on almost all scales during treatment. However, role and physical functioning recovered almost to the functioning level of the patient without chemotherapy or with early-stage disease after 12 months, suggesting that side effects of the chemotherapy on certain functioning outcomes recover completely or for a large part after the end of treatment. These findings correspond to previous research which found that the HRQoL of patients receiving chemotherapy was poorer during chemotherapy, but they experienced a larger improvement than patients without chemotherapy [25]. As patients with an advanced tumor stage often receive (neo)adjuvant treatment, results of chemotherapy and disease stage are probably related to one another [26]. Similar to earlier findings, cognitive functioning remained impaired for ovarian cancer patients after chemotherapy caused by long-term toxicity, while improvements were described in patients who did not receive chemotherapy [27].

Differences observed between endometrial and ovarian cancer patients are probably related to the prognosis of the disease, the different treatment modalities and its side-effects. This may explain why endometrial cancer patients initially have higher mean HRQoL scales than ovarian cancer patients, resulting in smaller improvements in HRQoL among endometrial cancer patients over time. This may also explain why ovarian cancer patients receiving chemotherapy have worse HRQoL than those who did not.

The strengths of this study include the longitudinal design, the limited in- and exclusion criteria and the high response rates (70–75%), allowing to observe changes over time and to ensure generalizability of the results. Further, to correct for false positive finding (type 1 error) the Bonferroni correction for multiple testing was used, thereby limiting the probability to find significant results due to chance [28]. However, several limitations should be considered. Postal codes were used to determine the SES of the patients, which might not be fully reliable since postal codes cover a large area of the municipality which may include a broad range of SES [29]. Thus, individual patients could be misallocated within the SES category. The loss to follow-up was observed, which could lead to attrition bias [30]. Patients who were

lost to follow-up were on average older and received more often chemotherapy compared to their counterparts that completed all questionnaires, which may be explained by death or ill-health. In addition, endometrial cancer patients who were lost to follow-up had more often multiple comorbidities and less often a partner. Therefore, our study population may be of higher general health and less severe side effects of the treatment, causing an overestimation of the improvements in HRQoL. However, the results of our sensitivity analysis only including patients that were not lost to follow-up led to similar conclusions. Furthermore, we excluded those with progressive disease and the follow-up data at the point of recurrence because we aimed to assess HRQoL in a disease-free population. Therefore, our results may not be generalizable to patients with progressive disease or recurrence. Further, results may not be generalizable to other (gynecological) cancer types because of different treatment regimens and side effects. These populations may have other patterns of HRQoL and different needs, which requires future research in these patients. Another limitation is that questionnaires were completed after initial treatment, but sometimes during adjuvant therapy (endometrial $n = 25$; ovarian $n = 79$), resulting in heterogeneous responses at the first questionnaire. Also, our study did not include a baseline assessment of HRQoL before treatment, and patients were followed for 24 months. Future research is needed to provide a more complete assessment of changes in HRQoL starting right after diagnosis until long-term follow-up. Furthermore, other important factors may be important in explaining changes in HRQoL, including sexual functioning, body image, personality and depression, which require further investigation [5,31].

The HRQoL of patients gained more importance over the last decades after the survivors' population has been growing [4]. Improvements in HRQoL were seen in some subgroups of patients, however, others continued to experience impairments. Insight into these subgroups of patients might help determine which patients are in need of additional support. Support might be offered to those who have trouble regaining full functioning after six months. Alternatively, we might want to improve our ability to better predict recovery and offer tailored support for those in need already shortly after the end of treatment. As suggested by our findings, individually tailored follow-up care should also be provided to patients with multiple comorbidities, ovarian cancer patients who receive chemotherapy and have advanced stage cancer, and endometrial cancer patients who do not receive radiotherapy. Routine assessment of patient-reported outcomes such as HRQoL is a promising tool for monitoring patients' health in clinical practice. Value-based health care may help to timely address patients' needs [32]. However, longitudinal studies are needed to understand the deterioration in role- and physical functioning of endometrial cancer patients and to identify subgroups of patients that are in highest need of supportive care.

In conclusion, endometrial- and ovarian cancer patients reported improved HRQoL within 6 months after initial treatment. However, some subgroups of patients, including those with multiple comorbidities, with an advanced tumor stage and after receiving chemotherapy, may be in need of additional support as they are less likely to show improvements in HRQoL over time. Future research should try to identify those who do not recover by themselves and may thus be in need for additional support.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The ROGY Care trial is supported with grant no. UVT 2010-4743 from the Dutch Cancer Society. Dr. Nicole Ezendam was supported by a Fellowship grant from the Dutch Cancer Society [#UVT-2014-6632].

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