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Adjuvant treatment for endometrial cancer: efficacy, toxicity and quality of life

Boer, S.M. de

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A watercolor illustration of a landscape. The top half is dominated by deep blue and purple washes, suggesting a sky or a body of water. Below this, there are layers of yellow, orange, and light blue, creating a sense of depth and texture. A small, dark figure of a person is visible on a path that winds through the lower part of the illustration. The overall style is soft and artistic.

Chapter 4

Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial

Stephanie M. de Boer, Melanie E. Powell, Linda Mileskin, Dionyssios Katsaros, Paul Bessette, Christine Haie-Meder, Petronella B. Ottevanger, Jonathan A. Ledermann, Pearly Khaw, Alessandro Colombo, Anthony Fyles, Marie-Helene Baron, Henry C. Kitchener, Hans W. Nijman, Roy F. Kruitwagen, Remi A. Nout, Karen W. Verhoeven-Adema, Vincent T.H.B.M. Smit, Hein Putter, Carien L. Creutzberg, on behalf of the PORTEC study group

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ABSTRACT

Background

About 15% of patients with endometrial cancer have high-risk features and are at increased risk of distant metastases and endometrial cancer-related death. We designed the PORTEC-3 trial to investigate the benefit of adjuvant chemoradiotherapy compared with radiotherapy alone for women with high-risk endometrial cancer.

Methods

PORTEC-3 was a multicentre, open-label, randomised, international trial. Women with high-risk endometrial cancer were randomly allocated (1:1) to radiotherapy alone (48.6 Gy) in 1.8 Gy fractions five times a week or chemoradiotherapy (two cycles concurrent cisplatin 50 mg/m² and four adjuvant cycles of carboplatin area under the curve [AUC] 5 and paclitaxel 175 mg/m²) using a biased coin minimisation procedure with stratification for participating centre, lymphadenectomy, stage of cancer, and histological type. The primary endpoints of the PORTEC-3 trial were overall survival and failure-free survival analysed in the intention-to-treat population. This analysis focuses on 2-year toxicity and health-related quality of life as secondary endpoints; analysis was done according to treatment received. Health-related quality of life was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) the cervix cancer module and chemotherapy and neuropathy subscales of the ovarian cancer module at baseline, after radiotherapy and at 6, 12, 24, 36, and 60 months after randomisation. Adverse events were graded with Common Terminology Criteria for Adverse Events version 3.0. The study was closed on Dec 20, 2013, after achieving complete accrual, and follow-up remains ongoing for the primary outcomes analysis. This trial is registered with ISRCTN.com, number ISRCTN14387080, and with ClinicalTrials.gov, number NCT00411138.

Findings

Between Sept 15, 2006, and Dec 20, 2013, 686 women were randomly allocated in the PORTEC-3 trial. Of these, 660 met eligibility criteria, and 570 (86%) were evaluable for health-related quality of life. Median follow-up was 42.3 months (IQR 25.8–55.1). At completion of radiotherapy and at 6 months, EORTC QLQ-C30 functioning scales were significantly lower (worse functioning) and health-related quality of life symptom scores higher (worse symptoms) for the chemoradiotherapy group compared with radiotherapy alone, improving with time. At 12 and 24 months, global health or quality of life was similar between groups, whereas physical functioning scores remained slightly lower in patients who received chemoradiotherapy compared with patients who received radiotherapy alone. At 24 months, 48 (25%) of 194 patients in the chemoradiotherapy

group reported severe tingling or numbness compared with 11 (6%) of 170 patients in the radiotherapy alone group ($p < 0.0001$). Grade 2 or worse adverse events were found during treatment in 309 (94%) of 327 patients in the chemoradiotherapy group versus 145 (44%) of 326 patients in the radiotherapy alone group, and grade 3 or worse events were found in 198 (61%) of 327 patients in the chemoradiotherapy group versus 42 (13%) of 326 patients in the radiotherapy alone group ($p < 0.0001$), with most of the grade 3 adverse events being haematological (45%). At 12 and 24 months, no significant differences in grade 3 or worse adverse events were found between groups; only grade 2 or higher sensory neuropathy adverse events persisted at 24 months (25 [10%] of 240 patients in the chemoradiotherapy group vs one [$< 1\%$] of 247 patients in the radiotherapy alone group; $p < 0.0001$).

Interpretation

Despite the increased physician and patient-reported toxicities, this schedule of adjuvant chemotherapy given during and after radiotherapy in patients with high-risk endometrial cancer is feasible, with rapid recovery after treatment, but with persistence of patient-reported sensory neurological symptoms in 25% of patients. We await the analysis of primary endpoints before final conclusions are made.

Funding

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INTRODUCTION

Endometrial cancer is most commonly diagnosed at an early stage and most women are cured with surgery alone.¹ Adjuvant treatment for early stage endometrial cancer is based on risk factors, such as histological grade, myometrial invasion, age, and lymph-vascular space invasion.²⁻⁴ The PORTEC-2 trial^{5,6} showed the efficacy of vaginal brachytherapy in reducing vaginal recurrence of endometrial cancer in women with high-intermediate-risk endometrial cancer. About 15% of all patients with endometrial cancer have high-risk disease (classified as stage I grade 3 cancer with deep invasion or with substantial lymph-vascular space invasion, stage II or III cancer, or cancer with non-endometrioid histology).¹ Higher incidence of distant metastases and endometrial cancer-related deaths has been reported for these patients.⁷⁻¹⁰ Serous and clear cell endometrial cancer are histological subtypes with poorer prognosis because of their high risk of metastasis, but when diagnosed at an early stage seem to have similar survival rates to grade 3 endometrioid endometrial cancer.¹¹

Pelvic external beam radiotherapy has been the standard adjuvant treatment for women with high-risk endometrial cancer for several decades. Randomised trials^{12,13} comparing adjuvant chemotherapy with external beam radiotherapy have shown similar rates of relapse and survival. Because increased pelvic relapse has been reported with adjuvant chemotherapy alone, use of pelvic radiotherapy combined with adjuvant chemotherapy has been advocated.^{14,15} The RTOG9708 phase 2 trial¹⁶ investigated a combination of external beam radiotherapy with two cycles of cisplatin, followed by four cycles of cisplatin-paclitaxel in 46 women with high-risk endometrial cancer. 4-year overall survival was 85% and disease-free survival was 81%, and acceptable toxicity was reported. The randomised NSGO-EC-9501/EORTC-55991 trial compared external beam radiotherapy alone with external beam radiotherapy and four cycles of platinum-based chemotherapy. This trial was published in a pooled analysis with the MaNGO ILIAD-III trial¹⁷ with a combined total of 534 patients, and showed statistically significantly improved progression-free survival with the addition of chemotherapy. None of these trials have reported detailed toxicity or quality of life data for chemoradiotherapy in endometrial cancer. Establishing both the benefit of more intensive adjuvant treatment and the effect in terms of added morbidity and effect on health-related quality of life are essential.

We initiated the international PORTEC-3 trial to investigate survival benefit and toxicities of chemotherapy combined with external beam radiotherapy compared with external beam radiotherapy alone for high-risk endometrial cancer. Final analysis of overall survival and failure-free survival is awaited, as the required number of events has not yet been reached. We did this analysis to establish and compare adverse events and patient-reported symptoms and health-related quality of life in women with high-risk endometrial cancer treated in PORTEC-3.

METHODS

Study design and participants

PORTEC-3 was a multicentre, open-label, randomised intergroup trial led by the Dutch Gynaecological Oncology Group. Patients were enrolled in the study by the radiation oncologists from the participating centres in the following international participating groups: the Medical Research Council and the National Cancer Research Institute (UK), the Australia New Zealand Gynaecological Oncology Group (Australia and New Zealand), Mario Negri Gynecologic Oncology group (Italy), Fedegyn (France) and National Cancer Institute of Canada Clinical Trials Group (Canada).

Patients were eligible for inclusion in this trial if they had International Federation of Gynecology and Obstetrics 2009 categorised stage IA grade 3 endometrial carcinoma with myometrial invasion and with documented lymph-vascular space invasion; stage IB grade 3; stage II, stage IIIA, or IIIC (or IIIB if parametrial invasion only); serous or clear cell histology with stage IA (with invasion), IB, II, or III. Eligible patients also had to have adequate WHO performance scores (WHO score 0–2); bone marrow (white blood cell count $\geq 3.0 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$); liver function (bilirubin $\leq 1.5 \times$ upper limit of normal [ULN], aspartate aminotransferase concentration $\leq 2.5 \times$ ULN, or alanine aminotransferase concentration $\leq 2.5 \times$ ULN); and kidney function (creatinine clearance >60 mL/min calculated according to Cockcroft¹⁸ or >50 mL/min EDTA clearance) and be aged older than 18 years. Exclusion criteria were having uterine sarcoma, previous malignancy less than 10 years ago, receipt of previous pelvic radiotherapy, hormonal or chemotherapy, gross cervical involvement with radical hysterectomy, inflammatory bowel disease, residual macroscopic tumour, impaired renal or cardiac function, neuropathy grade 2 or worse, hearing impairment grade 3 or worse, or congenital hearing disorder. Surgery comprised of total abdominal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy. Lymphadenectomy was left at the discretion of the participating centres. For serous or clear cell carcinoma, staging including omentectomy; peritoneal biopsies and lymph node sampling were recommended. Upfront central pathology review was undertaken by the reference gynaecological pathologists of the participating groups to confirm final eligibility for the study.

Written informed consent was obtained from all patients. The protocol was approved by the Dutch Cancer Society, and the ethics committees of the participating groups or centres. Participating groups obtained their institutional review board and ethics approvals and were funded by separate grants. The protocol is available online (www.clinicalresearch.nl/portec3).

Randomisation and masking

Patients were randomly allocated (1:1) to receive either chemoradiotherapy or radiotherapy alone. Treatment was allocated with a biased coin minimisation procedure, with stratification according to participating centre, lymphadenectomy (yes or no), stage, and histological type. The outcome of the allocation was computer generated and not predictable by the investigators. Patients were registered and randomised by the participating group's data centres and treatment was assigned with a web-based application. The trial number and assigned treatment were generated immediately by the randomisation programme and confirmed by email to the investigators. Participants and investigators were not masked to treatment allocation.

Procedures

Pelvic radiotherapy was given in both treatment groups (48.6 Gy in 1.8 Gy fractions, five times a week for 5.5 weeks). The clinical target volume included the proximal vagina, parametrial tissues, and internal, external, and common iliac lymph node regions up to the upper S1 level (the level of promontory). The clinical target volume was extended for lymph node involvement. In case of cervical involvement, a brachytherapy boost was given. Treatment had to be started preferably within 4–6 weeks after surgery, but no later than 8 weeks after surgery. Treatment breaks were avoided and could not exceed 2 days, overall treatment time for radiotherapy could not exceed 50 days.

Patients in the chemoradiotherapy group received two cycles of cisplatin 50 mg/m² in the first and fourth week of radiotherapy, followed by four cycles of carboplatin area under the curve (AUC) 5 and paclitaxel 175 mg/m² at 21-day intervals (and a 28-day interval between the second concurrent and first adjuvant cycle). This schedule was based on the RTOG9708 trial,¹⁶ with substitution of cisplatin with carboplatin in the adjuvant phase. In the event of haematological, renal, or other toxicities, cisplatin was postponed for 1 week. If recovery required more than 1 week or in the case of neurological adverse events of grade 2 or worse, cisplatin was discontinued. Carboplatin was postponed or stopped in the case of severe haematological toxicity. Carboplatin dose was reduced to AUC 4 if recovery to grade 1 was attained at two weeks. Paclitaxel was postponed if grade 2 neuropathy was reported and stopped if recovery exceeded 1 week or grade 3 neuropathy developed. After recovery or reduction to grade 1 adverse events, paclitaxel dose was reduced to 135 mg/m². Carboplatin and paclitaxel were delayed for other grade 3–4 toxicities, and discontinued if there was no recovery or reduction to grade 1 adverse events.

Patients were assessed every 3 months for the first 24 months, and every 6 months up to 5 years. Long-term outcome evaluation at 7 and 10 years was obtained, preferably by follow-up visits, or by information from their general practitioner. At each follow-up visit, a patient history with emphasis on treatment-related morbidity, and physical and pelvic

examination was done. Chest radiograph, blood count, and chemistry tests (including Ca-125) were obtained once a year, up to 5 years after randomisation.

Toxicity was graded with the Common Terminology Criteria for Adverse Events version 3.0 and was assessed at baseline (after surgery), completion of radiotherapy, at each chemotherapy cycle, and at 6-month follow-up intervals from randomisation until 5 years and at 7 and 10 years. Health-related quality of life questionnaires were completed at baseline after surgery and after completion of radiotherapy, at 6-month intervals from randomisation until 24 months, and at 36 and 60 months. Health-related quality of life was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, version 3.0).¹⁹ As the EORTC endometrial module was not yet available, the cervix 24 (CX24) module was used, with added chemotherapy and neuropathy subscales from the ovarian 28 (OV28) module.^{20,21} Higher scores on functional and global health-related quality of life scales represented better levels of functioning. On the symptom subscales, higher scores reflected higher levels of symptoms.

All adverse events were graded and adverse events of grade 2 or worse were reported on case record forms, irrespective of the relation with study treatment. For mild (grade 1) toxicities, the patient-reported health-related quality of life symptoms were used. Serious adverse events were reported within 24 h, specifying adverse event grade and relation to study treatment. Time from randomization was used to compare severity and duration of toxicities between the treatment groups; importantly, the 6-month timepoint was about 1 month after completion of chemotherapy in the chemoradiotherapy group.

Outcomes

Primary endpoints were overall survival and failure-free survival, with failure defined as any relapse or death related to endometrial carcinoma. Secondary endpoints were treatment-related toxicity, health-related quality of life, and pelvic or distant relapse.

Statistical analysis

The PORTEC-3 trial was powered (80%) to detect a difference of 10% (HR 0.67) in 5-year overall survival (65% to 75%); for this, 198 events were required, and a minimum of 655 patients. The analysis plan for the second primary endpoint failure-free survival will be added in an amendment to the trial protocol. Primary and secondary outcomes not involving toxicity or health-related quality of life were analysed by intention to treat. Safety outcomes were assessed in all patients who received at least one cycle of chemotherapy and 1 week of radiotherapy (in the chemoradiotherapy group) and 1 week of radiotherapy (in the radiotherapy alone group). Although no specific power calculations were done for the toxicity and health-related quality of life analysis, the minimum

required number of 655 patients ensured sufficient power to detect clinically relevant differences. Toxicity and quality of life were analysed according to treatment received. Formal tests for the differences in relapse and survival rates between the two groups were done with the Kaplan-Meier method, the log-rank test, and Cox regression analysis. The median follow-up of all patients was estimated by the inverse Kaplan-Meier method. We measured toxicity at baseline, at completion of radiotherapy, every cycle of concurrent and adjuvant chemotherapy, and 6, 12, 18, and 24 months; quality of life was measured at baseline, completion of radiotherapy, and 6, 12, 18, and 24 months after randomisation. During follow-up, toxicity and quality of life forms completed within a 3-month window before or after the designated timepoint were included. The time during treatment was defined as all toxicity forms related to radiotherapy and all cycles of concurrent and adjuvant chemotherapy.

Criteria to be removed from the analysis were ineligibility or withdrawal of informed consent before the start of treatment. Patients were evaluable for health-related quality of life analysis if they had completed baseline and at least one follow-up form. Missing data for patients were handled as missing-at-random, assuming that missing data was not related to the values of the unobserved variables. This is an assumption that is not possible to verify statistically.²² The prevalence of toxicity graded according to the Common Terminology Criteria for Adverse Events version 3.0 was calculated at each timepoint. Per adverse event, the maximum grade per patient was calculated (worst ever by patient). The maximum grade over the entire course of therapy and follow-up for any adverse events and for the individual patient was used as a summary of toxicity. Fisher's Exact test was used to compare toxicity between the two treatment groups. A prespecified health-related quality of life analysis was done according to the EORTC Quality of Life Group guidelines.²³ Baseline scores of both treatment groups were compared with a *t* test, or Armitage trend test for single items. A linear mixed model was used to obtain estimates of the EORTC QLQ-C30, CX24, and OV28 subscales at each of the timepoints, with patient as random effect and time (categorical), treatment, and their interaction between time and treatment as fixed effects. Single items were analysed with (binary) logistic regression with random effect, combining scores of 1–2 ("not at all" and "a little") and 3–4 ("quite a bit" and "very much"). The difference in health-related quality of life between the groups over time was tested by a joint Wald test of all treatment-by-time interaction in the linear or logistic mixed model. To guard against false-positive results because of multiple testing, a two-sided *p* value of less than or equal to 0.01 was considered statistically significant. Guidelines for the interpretation of clinically relevant changes to EORTC QLQ-C30 scores were applied.^{24,25} For scales not included in the guidelines, changes were assessed according to Osoba and colleagues.²⁶ Statistical analyses were done with SPSS, version 20.0, and R statistical software, version 3.2.1.

A Data and Safety Monitoring Board oversaw the study. After discussion within the trial management group and with approval of the Data and Safety Monitoring Board, the decision was made to submit for publication. The study was closed on Dec 20, 2013, after achieving complete accrual; follow-up is continuing. This trial is registered with ISRCTN.com, number ISRCTN14387080, and with ClinicalTrials.gov, number NCT00411138.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The central data manager (KWV-A), the principal investigator (CLC) and associated investigators (SMdB, RAN), and trial statistician (HP) had full access to the data. The Dutch Cancer Society Scientific Review Board approved the trial design. The corresponding author and chief investigator had full access to all of the data and the final responsibility to submit for publication.

RESULTS

Between Sept 15, 2006, and Dec 20, 2013, we recruited 686 patients to the PORTEC-3 trial. Of these patients, 13 did not meet inclusion criteria (figure 1). Reasons for exclusion were different stage, macroscopic residual disease, low creatinine clearance, impaired hearing (\geq grade 3), or different histological type. Another 13 patients withdrew their informed consent immediately after randomisation and were excluded from this analysis, leaving 660 patients (330 in each group) for intention-to-treat analysis. Seven (1%) of 660 patients refused the allocated treatment (five in the chemoradiotherapy group and two in the radiotherapy alone group) and switched to the other treatment group (figure 1). For analysis of toxicity and health-related quality of life these seven patients were assessed by treatment received, resulting in 327 patients in the chemoradiotherapy group and 333 patients in the radiotherapy alone group. Median follow-up at the time of analysis for all patients was 42.3 months (IQR 25.8–55.1); 42.1 months (25.7–54.7) in the chemoradiotherapy group and 42.4 months (27.1–55.4) in the radiotherapy alone group. With ongoing follow-up, 487 (74%) patients (240 in the chemoradiotherapy group and 247 in the radiotherapy alone group) had reached the 2-year timepoint by the time of this analysis. Patient characteristics were well balanced between the chemoradiotherapy and radiotherapy alone groups (table 1). Lymphadenectomy was performed in 203 (62%) in the chemoradiotherapy group and in 205 (62%) patients in the radiotherapy alone group. Radiotherapy was discontinued by one (<1%) patient who received chemoradiotherapy because of disease progression and by five (2%) patients who received radiotherapy alone because of toxicity (n=4) and an accidental fall with femur fracture (n=1). A brachytherapy boost was given in 149 (46%) of 327 patients in the chemoradio-

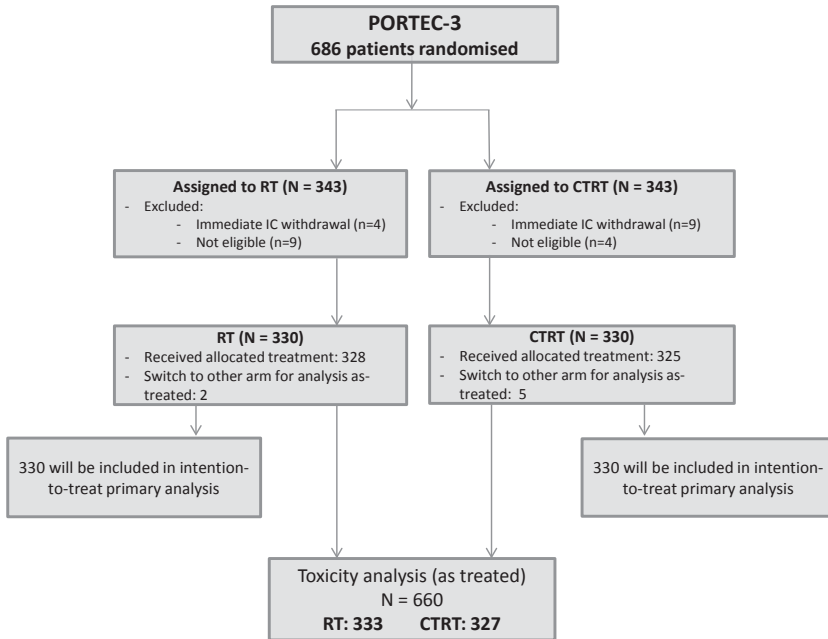


Figure 1. Trial profile

therapy group and 156 (47%) of 333 patients in the radiotherapy alone group. Treatment completion details are shown in table 1. Chemotherapy was discontinued in 61 (19%) patients because of drug-related toxicity in 31 (9%) patients, patient decision in 20 (6%) patients, disease progression in seven (2%) patients, or for other reasons in three (1%) patients. Dose reductions were reported if the dose was reduced by more than 10%. At least one dose reduction of cisplatin (to 40 mg/m²) was recorded for five (2%) patients, of carboplatin (from AUC 5 to AUC 4) for 22 (7%) patients, and of paclitaxel (from 175 mg/m² to 135 mg/m²) for 34 patients (10%). Analysis of primary outcomes is ongoing and will be reported in a future publication.

For 570 (86%) of 660 patients, a baseline questionnaire and at least one follow-up questionnaire was received, 292 for the chemoradiotherapy group and 278 in the radiotherapy alone group. These 570 responders were assessable for health-related quality of life. 90 (14%) of 660 patients could not be assessed for health-related quality of life, mostly because of a missing form at baseline, whereas some questionnaires were invalid because of missing dates of completion or a completion date after the first day of radiotherapy. At 24 months, health-related quality of life scores of 364 (55%) patients had been received, which corresponds to 64% of the 570 responders: (194 [66%] of 292 patients in the chemoradiotherapy group and 170 [61%] of 278 patients in the radiotherapy alone group). Questionnaire response rates for each timepoint are given

Table 1. Characteristics of as-treated population by treatment group

	Chemoradiotherapy (n = 327)		Radiotherapy alone (n = 333)	
	No. of patients	%	No. of patients	%
Age at randomisation (years)				
Median	62.5		61.9	
Interquartile range	56.5 - 68.0		55.9 - 68.1	
< 60 years	125	38%	143	43%
60-69 years	143	44%	129	39%
≥70 years	58	18%	61	18%
Missing data*	1		0	
FIGO 2009-stage				
Stage I	95	30%	97	31%
Stage II	79	25%	88	28%
Stage III	144	45%	131	41%
Missing data*	9		17	
Histologic grade and type				
EEC Grade 1	44	14%	45	14%
EEC Grade 2	81	25%	80	24%
EEC Grade 3	102	32%	111	34%
Non-endometrioid	83	26%	77	23%
Mixed	13	4%	17	5%
Missing data*	4		3	
WHO performance				
0 - 1	319	98%	327	98%
≥2	5	2%	5	2%
Missing data*	3		1	
Comorbidity				
Diabetes	45	14%	36	11%
Hypertension	115	35%	105	32%
Cardiovascular	30	9%	20	6%
Type of surgery				
Total abdominal hysterectomy and bilateral salpingo-oophorectomy	82	25%	87	26%
Total abdominal hysterectomy and bilateral salpingo-oophorectomy plus lymph node dissection or full staging (lymph node dissection with omentectomy and peritoneal biopsies)	153	47%	146	44%
Total laparoscopic hysterectomy and bilateral salpingo-oophorectomy	41	13%	40	12%
Total laparoscopic hysterectomy and bilateral salpingo-oophorectomy plus lymph node dissection or full staging (lymph node dissection with omentectomy and peritoneal biopsies)	50	15%	59	18%
Missing data*	1		1	

Table 1. Characteristics of as-treated population by treatment group (*continued*)

	Chemoradiotherapy (n = 327)		Radiotherapy alone (n = 333)	
	No. of patients	%	No. of patients	%
Treatment completion				
Radiotherapy	326 (100%)		328 (98%)	
Brachytherapy boost	149 (46%)		156 (47%)	
1 cycle Cisplatin	325 (99%)		-	
2 cycles Cisplatin	305 (93%)		-	
1 cycle Carboplatin/Paclitaxel	303 (93%) / 303 (93%)		-	
2 cycles Carboplatin/Paclitaxel	295 (90%) / 295 (90%)		-	
3 cycles Carboplatin/Paclitaxel	279 (85%) / 267 (82%)		-	
4 cycles Carboplatin/Paclitaxel	262 (80%) / 235 (72%)		-	

Data are median (IQR) or n (%). *Missing values are not included in the percentage calculation. FIGO=International Federation of Gynaecology and Obstetrics. EEC=endometrioid endometrial carcinoma.

Table 2. Toxicity reported by physicians using the CTCAE v3.0 during treatment and follow-up.

	Maximum grade per patient during treatment CTRT n=327; RT n=326					
	Grade 2		p*	Grade 3-4		p#
	CTRT n (%)	RT n (%)		CTRT n (%)	RT n (%)	
Any	111 (34)	102 (31)	<0.0001	198 (61)	42 (13)	<0.0001
Any grade 3	na	na		149 (46)	42 (13)	
Any grade 4	na	na		49 (15)	0 (0)	
Auditory/hearing	14 (4)	3 (1)	0.011	1 (<1)	1 (<1)	
Fatigue	70 (21)	7 (2)	<0.0001	10 (3)	0 (0)	0.0018
Alopecia	185 (57)	1 (<1)	<0.0001	na	na	
Any gastrointestinal	145 (44)	79 (24)	<0.0001	47 (14)	18 (6)	0.0002
Diarrhea	103 (31)	69 (21)	<0.0001	35 (11)	13 (4)	0.0014
Ileus/obstruction	3 (1)	5 (2)		2 (1)	2 (1)	
Nausea	68 (21)	24 (7)	<0.0001	9 (3)	2 (1)	0.063
Any haematological	99 (30)	19 (6)	<0.0001	148 (45)	18 (6)	<0.0001
Febrile neutropenia	na	na		9 (3)	1 (<1)	0.021
Infection with neutropenia	3 (1)	0 (0)	0.0018	7 (2)	0 (0)	0.015
Infection without neutropenia	21 (6)	1 (<1)	<0.0001	12 (4)	0 (0)	0.0004
Any neuropathy	78 (24)	1 (<1)	<0.0001	23 (7)	0 (0)	<0.0001
Motor neuropathy	13 (4)	1 (<1)	0.0001	4 (1)	0 (0)	
Sensory neuropathy	75 (23)	0 (0)	<0.0001	22 (7)	0 (0)	<0.0001
Any pain	101 (31)	23 (7)	<0.0001	31 (9)	4 (1)	<0.0001
Genitourinary incontinence	11 (3)	5 (2)		1 (<1)	0 (0)	
Genitourinary urinary frequency	22 (7)	10 (3)	0.041	2 (1)	2 (1)	
Thrombosis or embolism	2 (1)	0 (0)	0.031	4 (1)	0 (0)	

AE were calculated at each time point. Per AE, the maximum grade per patient was calculated (worst ever by patient). p* = significant level < 0.01 for grade 2, 3 and 4; p# = significant level < 0.01 for grade 3 and 4. Only p-values ≤ 0.10 were listed.

in the appendix (Table S1). WHO performance score was different between those who responded to the questionnaire and those who did not, with WHO 0–1 recorded in 565 (99%) of 570 patients who responded versus 85 (94%) of 90 patients who did not respond, and WHO score of 2 or more in five (1%) patients who responded versus five (6%) patients who did not respond ($p=0.007$). No other differences were seen in patient characteristics between responders and non-responders (data not shown). 89% of the responders completed all items of the EORTC QLQ-C30 in the returned questionnaires, 80% completed all items of the CX24 subscale, 92% completed all non-sexual items, and 91% of the responders completed all items of the OV28 subscale.

Adverse event incidence during and after treatment is summarised in table 2. A comprehensive list of adverse events is provided in the appendix (Table S3). At baseline, no significant differences in adverse events were recorded between groups. Baseline grade 2 adverse events were reported for 109 (33%) of 327 patients who received chemoradiotherapy and 93 (29%) of 326 patients who received radiotherapy alone, and grade 3–4

Maximum grade per patient at 6 months CTRT n=327; RT n=324						Maximum grade per patient at 12 months CTRT n=305; RT n=304					
Grade 2			Grade 3-4			Grade 2			Grade 3-4		
CTRT n (%)	RT n (%)	p*	CTRT n (%)	RT n (%)	p#	CTRT n (%)	RT n (%)	p*	CTRT n (%)	RT n (%)	p#
128 (39)	95 (29)	<0.0001	55 (17)	25 (8)	0.0005	102 (33)	87 (29)	0.058	33 (11)	22 (7)	
na	na		49 (15)	21 (6)		na	na		28 (9)	20 (7)	
na	na		6 (2)	4 (1)		na	na		5 (2)	2 (1)	
8 (2)	3 (1)		0 (0)	0 (0)		10 (3)	2 (1)	0.037	0 (0)	0 (0)	
9 (3)	2 (1)	0.055	1 (<1)	1 (<1)		5 (2)	4 (1)		0 (0)	2 (1)	
64 (20)	0 (0)	<0.0001	na	na		0 (0)	2 (1)		na	na	
19 (6)	17 (5)		7 (2)	9 (3)		21 (7)	19 (6)		7 (2)	2 (1)	
8 (2)	11 (3)	0.1	0 (0)	3 (1)		11 (4)	8 (3)		1 (<1)	1 (<1)	
1 (0)	1 (0)		7 (2)	8 (2)		2 (1)	3 (1)		4 (1)	2 (1)	
7 (2)	5 (2)		5 (2)	2 (1)		3 (1)	2 (1)		1 (0)	0 (0)	
54 (17)	27 (8)	<0.0001	24 (7)	6 (2)	0.001	26 (9)	20 (7)		4 (1)	7 (2)	
na	na		0 (0)	0 (0)		na	na		0 (0)	0 (0)	
0 (0)	0 (0)		1 (<1)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
5 (2)	1 (<1)		0 (0)	0 (0)		1 (<1)	3 (1)		1 (<1)	0 (0)	
42 (13)	1 (<1)	<0.0001	8 (2)	2 (1)		26 (9)	2 (1)	<0.0001	4 (1)	1 (<1)	
7 (2)	1 (<1)	0.089	3 (1)	2 (1)		1 (0)	0 (0)		3 (1)	1 (<1)	
42 (13)	0 (0)	<0.0001	6 (2)	0 (0)	0.031	26 (9)	2 (1)	<0.0001	4 (1)	1 (<1)	
31 (9)	30 (9)		3 (1)	7 (2)		27 (9)	21 (7)		8 (3)	4 (1)	
6 (2)	7 (2)		1 (<1)	0 (0)		8 (3)	9 (3)		1 (<1)	1 (<1)	
5 (2)	6 (2)		0 (0)	0 (0)		4 (1)	8 (3)		0 (0)	1 (<1)	
3 (1)	0 (0)		2 (1)	1 (<1)		1 (<1)	0 (0)		0 (0)	1 (<1)	

toxicities were reported in 33 (10%) patients who received chemoradiotherapy and 28 (9%) patients who received radiotherapy alone. No deaths occurred during treatment; two patients (one in each group) died shortly after treatment: one patient in the chemoradiotherapy group died from pneumonia after surgery for bowel obstruction because of adhesions; one elderly patient in the radiotherapy alone group died 3 weeks after radiotherapy because of pneumonia and subsequent multiorgan failure. The death of both patients was not related to the study treatment as reported by the treating physician.

During the study, including whole treatment and follow-up period, 89 (27%) of 327 patients in the chemoradiotherapy group versus 154 (47%) of 326 patients in the radiotherapy alone group had a maximum toxicity of grade 2 adverse events. Grade 3 adverse events or worse were reported for 229 (70%) of 327 patients in the chemoradiotherapy group versus 112 (34%) of 326 patients in the radiotherapy alone group (figure 2). During treatment, grade 2 or worse adverse events were found in 309 (94%) of 327 patients in the chemoradiotherapy group versus 145 (44%) of 326 patients in the radiotherapy alone group ($p < 0.0001$); grade 3 or higher were found in 198 (61%) patients in the chemoradiotherapy group versus 42 (13%) patients in the radiotherapy alone group ($p < 0.0001$; figure 2, table 2). Most grade 3 or worse toxicities in both groups during treatment were haematological, gastrointestinal, or pain related. During treatment, grade 3 or worse sensory neuropathy was reported in 22 (7%) patients and motor neuropathy was reported in four (1%) patients, all in the chemo radiotherapy group. At 12 and 24 months after treatment, no significant difference in grade 3 or worse adverse events was seen between the groups.

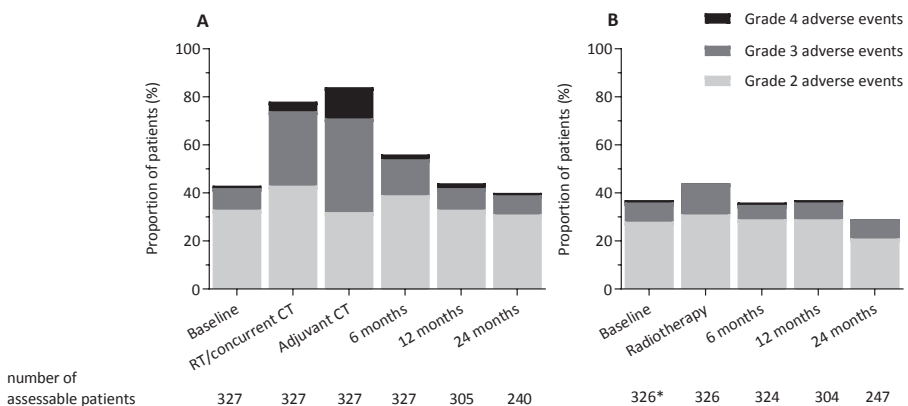


Figure 2. Incidence of the maximum physician-reported adverse event grades per patient for each time-point at baseline, during treatment and at 6, 12, and 24 months follow-up in the chemoradiotherapy group (A) and the radiotherapy alone group (B)

*Total not 333 because of missing forms.

The most important persisting toxicity was grade 2 or worse sensory neuropathy at 12 months in 30 (10%) patients in the chemoradiotherapy group versus three (1%) patients in the radiotherapy group, and 25 (10%) patients in the chemoradiotherapy group versus one (<1%) patient in the radiotherapy alone group at 24 months ($p < 0.0001$). No significant differences in gastrointestinal, genitourinary, or haematological toxicities were seen at 12 and 24 months. Slightly worse auditory toxicity and bone-related pain were found in patients treated with chemoradiotherapy at 12 months (appendix Table S3).

Results of the EORTC QLQ-C30 functioning subscales and global health status, and mean scores for CX24 and OV28 subscales are summarised in table 3. All single symptom items are reported in appendix (Table S4). During treatment, patients treated with chemoradiotherapy scored significantly lower on most EORTC functioning scales; 10–20-point lower scores on physical, role, and social functioning, and global health status compared with patients treated with radiotherapy alone. However, rapid recovery was reported,

Table 3. Patient-reported health-related quality of life symptoms using the EORTC QLQ-C30 and subscales of CX-24 and OV-28 over the treatment and two-year follow up

	Questionnaire time points						p-value		
	Baseline	After RT	Months				Changes over time	Difference between groups	Differences between groups over time
			6	12	18	24			
EORTC functioning scales									
Physical functioning									
Chemoradiotherapy	81.3	76.3	72.5	80.1	79.5	80.0	<0.0001	<0.0001	<0.0001
Radiotherapy	84.6	83.1	86.5	85.9	84.8	85.5			
Role functioning									
Chemoradiotherapy	70.4	66.5	67.8	79.3	78.7	79.8	<0.0001	<0.0001	<0.0001
Radiotherapy	73.7	74.5	84.7	85.1	83.7	85.8			
Emotional functioning									
Chemoradiotherapy	74.4	76.9	77.1	79.1	80.3	81.1	<0.0001	0.21	0.74
Radiotherapy	77.6	81.7	80.6	82.2	82.0	84.7			
Cognitive functioning									
Chemoradiotherapy	87.0	81.8	79.8	84.5	82.8	85.1	<0.0001	0.002	0.008
Radiotherapy	88.0	85.6	86.9	86.8	86.2	85.7			
Social functioning									
Chemoradiotherapy	78.1	73.5	74.4	84.2	85.4	85.4	<0.0001	<0.0001	<0.0001
Radiotherapy	80.4	78.7	88.3	89.0	87.7	91.2			
Global health status/ Quality of Life									
Chemoradiotherapy	86.2	77.3	81.8	89.8	87.3	89.6	<0.0001	<0.0001	<0.0001
Radiotherapy	87.1	85.3	89.6	90.1	90.7	90.5			

Table 3. Patient-reported health-related quality of life symptoms using the EORTC QLQ-C30 and subscales of CX-24 en OV-28 over the treatment and two-year follow up (continued)

	Questionnaire time points						p-value		
	Baseline	After RT	Months				Changes over time	Difference between groups	Differences between groups over time
			6	12	18	24			
EORTC symptom scales									
Fatigue									
Chemoradiotherapy	28.9	42.0	38.4	27.7	28.9	26.9	<0.0001	<0.0001	<0.0001
Radiotherapy	26.5	34.1	23.7	23.7	22.7	22.5			
Nausea and vomiting									
Chemoradiotherapy	3.8	14.1	8.8	4.7	3.8	3.5	<0.0001	<0.0001	<0.0001
Radiotherapy	4.0	10.0	5.5	6.9	4.8	6.7			
Pain									
Chemoradiotherapy	18.4	21.2	23.3	20.8	19.9	19.0	0.06	0.09	0.24
Radiotherapy	17.0	19.6	16.6	16.6	16.0	16.7			
CX 24 subscales									
Symptom experience [*]									
Chemoradiotherapy	9.6	16.2	12.1	11.6	11.9	11.7	<0.0001	0.66	0.55
Radiotherapy	9.5	16.8	12.1	12.6	11.1	11.9			
Body image									
Chemoradiotherapy	11.6	16.6	24.9	16.0	15.0	15.6	<0.0001	<0.0001	<0.0001
Radiotherapy	9.9	12.8	12.7	12.4	11.6	11.2			
Sexual functioning [†]									
Chemoradiotherapy	13.2	22.3	18.3	19.9	17.2	21.4	0.05	0.36	0.34
Radiotherapy	9.5	22.4	22.0	23.6	22.7	25.5			
OV 28 subscales									
Chemotherapy [‡]									
Chemoradiotherapy	7.9	18.7	31.2	14.7	14.0	13.2	<0.0001	<0.0001	<0.0001
Radiotherapy	6.2	11.2	12.1	12.5	12.3	11.5			
Peripheral neuropathy									
Chemoradiotherapy	5.5	14.2	47.0	31.4	28.5	27.8	<0.0001	<0.0001	<0.0001
Radiotherapy	5.5	8.8	12.8	12.9	12.6	13.2			

All subscales responses were converted to 0 to 100 scales (according to the EORTC guidelines). Higher scores for functioning items and global quality of life scale represent a better level of functioning. For the symptom scales, a higher score reflects a higher level of symptoms. EORTC QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. CX24=cervix 24. OV28=ovarian 28. *Subscale symptom experience included abdominal cramps, controlling bowels, blood in stool, urinary frequency, dysuria, urinary incontinence, difficulty emptying bladder, lower back pain, vaginal irritation or soreness, vaginal discharge, and abnormal vaginal bleeding. †Responses to the questions of this subscale were only expected if the respondent was indicated to be sexually active. ‡Subscale chemotherapy included hair loss, taste change, muscle aches or pains, hearing problems, urinary frequency, or skin problems.

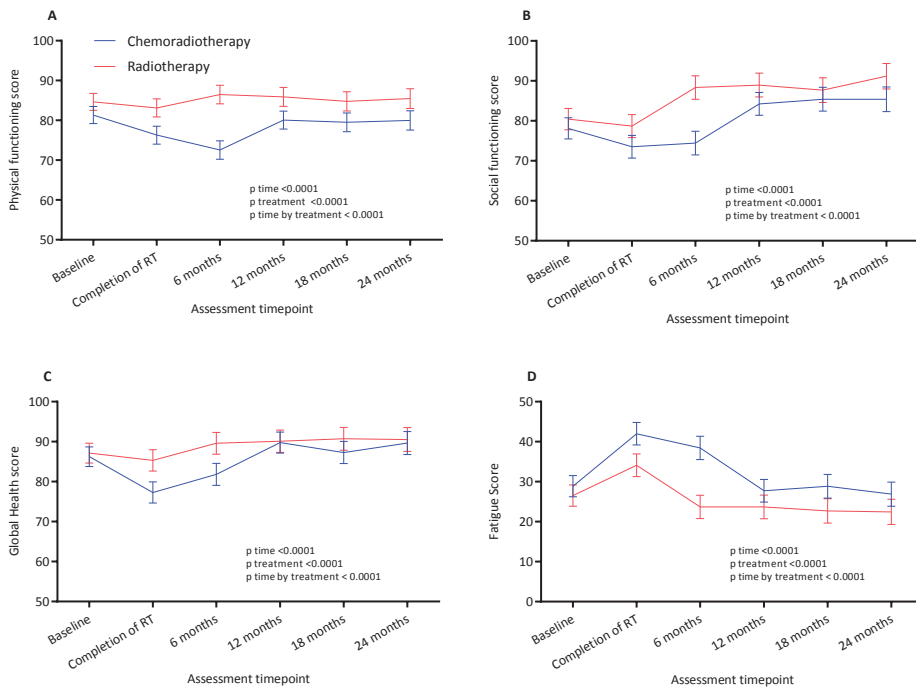


Figure 3. Patient functioning subscales and single-item symptom EORTC QLQ-C30 scores for physical functioning (A), social functioning (B), global health status or quality of life (C), and fatigue (D). For physical functioning, social functioning, and global health status or quality of life, a higher score indicated a higher level of functioning or activity, and for fatigue, a higher score indicates a higher level of symptoms. Error bars show 95% CI. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. p time=difference in quality of life scores over time within the whole treatment group. p treatment=difference between the two treatment groups. p time by treatment=difference between the two treatment groups over time.

and at 12 months physical functioning was the only significant difference between the two treatment groups (figure 3).

The most frequently reported severe (“quite a bit” or “very much”) symptoms at 6 months were tingling or numbness in 111 (52%) of 214 patients in the chemoradiotherapy group versus 15 (7%) of 209 patients in the radiotherapy alone group ($p < 0.0001$), muscle or joint pain in 80 (37%) of 214 patients in the chemoradiotherapy group versus 45 (22%) of 207 patients in the radiotherapy alone group ($p = 0.002$), fatigue in 66 (31%) of 210 patients versus 36 (17%) patients ($p = 0.0004$), weakness in the arms or legs in 76 (36%) of 214 patients versus 24 (11%) of 209 patients ($p < 0.0001$), and hair loss in 88 (44%) of 200 patients versus eight (4%) of 208 patients ($p < 0.0001$), with events in the chemoradiotherapy group significantly higher in all these cases. At 24 months, most differences had subsided and the most frequent symptoms did not differ much from baseline (figure 4).

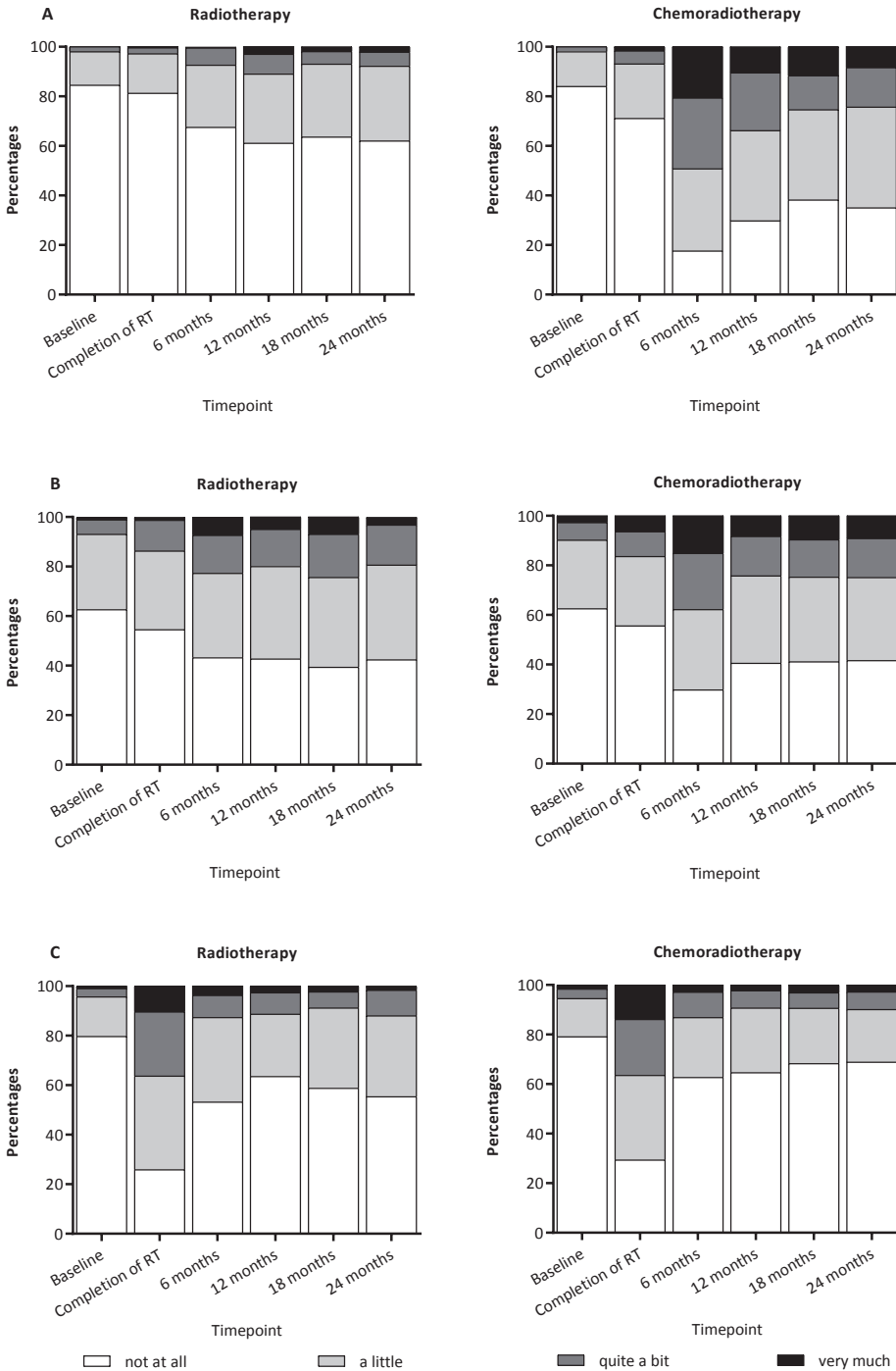


Figure 4. Patient responses on single-item symptom scales over time for tingling or numbness (A), muscle or joint pain (B), and diarrhoea (C) in the chemoradiotherapy group and the radiotherapy alone group

Tingling or numbness was still significantly higher in patients in the chemoradiotherapy group (48 [25%] of 194 vs 11 [6%] of 170 patients; $p < 0.0001$).

Patient-reported lymphoedema did not differ between the two treatment groups (appendix Table S4). Severe lymphoedema was reported more frequently by patients who had undergone a lymphadenectomy (both treatment groups combined): 47 (17%) of 276 patients after lymphadenectomy versus 13 (8%) of 163 patients without lymphadenectomy at 12 months ($p = 0.01$) and 38 (16%) of 237 patients versus 14 (11%) of 127 patients at 24 months ($p = 0.2$). After lymphadenectomy, severe lymphoedema was reported by 18 (15%) of 120 patients in the chemoradiotherapy group and 20 (17%) of 117 patients in the radiotherapy alone group at 24 months ($p = 0.84$), compared with seven (10%) of 69 patients and seven (12%) of 58 patients, respectively, who had no lymphadenectomy ($p = 0.69$; appendix, Figure S2).

No significant differences in sexual functioning score were seen between the treatment groups, measured according to CX24 (table 3). Sexual activity was low in both groups, but was slightly higher in the radiotherapy alone group during treatment ($p = 0.006$), and similar thereafter (see appendix Table S4).

DISCUSSION

This analysis of toxicity and 2-year health-related quality of life in the PORTEC-3 trial for women with high-risk endometrial cancer clearly shows that adjuvant chemotherapy given during and after pelvic radiotherapy causes significantly higher incidence of severe adverse events and of patient-reported symptoms, and a decreased level of patient functioning and health-related quality of life compared with radiotherapy alone. However, rapid recovery was seen, with reduction of all incidence and grades of adverse events between 6 and 12 months after randomisation, and without significant differences in grade 3 or worse adverse events at 12 and 24 months. The only remaining significant difference in adverse events at 12 and 24 months was increased grade 2 or worse sensory neuropathy in the chemoradiotherapy group compared with the radiotherapy alone group (25 [10%] of 240 vs 1 [$< 1\%$] of 247), with health-related quality of life showing “quite a bit” or “very much” tingling or numbness reported by 25% of patients in the chemoradiotherapy group versus 6% of patients in the radiotherapy alone group. After 24 months, patients treated with chemoradiotherapy group still had slightly lower physical functioning scores, which might partly be because of their higher rate of peripheral neuropathy. Most functioning scores showed small remaining differences (0–6 points) in mean scores, which are of borderline clinical relevance according to the guidelines for interpretation of the EORTC QLQ-C30.^{24,25}

Patients treated in the chemoradiotherapy group reported significantly more tingling or numbness, muscle or joint pain, fatigue, weakness in the arms and legs, and hair loss at 6 months. All of these items, together with a longer treatment duration and more intense treatment because of the chemotherapy could be contributing to lower quality of life scores. The association between individual symptoms and overall quality of life will be a subject of further investigation.

The 6-month timepoint when most severe adverse events and worst quality of life were reported by patients receiving chemoradiotherapy was only 1 month after completion of chemotherapy, whereas patients treated with radiotherapy alone already had 4 months of recovery time. These results represent the toxicity profiles of the patients in the two treatment groups and provide a realistic view of the time with toxicity in the chemoradiotherapy group, which is of relevance for patient counselling when considering chemotherapy.

Data for the toxicity of chemotherapy in advanced or metastatic endometrial cancer are mainly available from the randomised trials²⁷ in which doxorubicin and cisplatin with or without paclitaxel were used. Incidence of sensory neuropathy in those trials during chemotherapy was significantly higher than in the PORTEC-3 trial, with 27% of patients having grade 2 adverse events and 12% of patients having grade 3 neuropathy when treated with the doxorubicin, cisplatin, and paclitaxel triplet combination. Results of the randomised GOG-209²⁸ trial in which the triplet chemotherapy was compared with carboplatin-paclitaxel are pending, but an abstract reported similar efficacy with a better toxicity profile of carboplatin-paclitaxel (NCT00063999). The GOG-249 trial²⁹ compared pelvic radiotherapy alone with vaginal brachytherapy followed by three cycles of carboplatin and paclitaxel in patients with stage I–II endometrial cancer with high-intermediate-risk or high-risk features. First results at a median follow-up of 24 months showed no differences in recurrence-free and overall survival, with more acute toxicity in the chemotherapy group. Data for health-related quality of life are pending.

Data for toxicity and health-related quality of life of women treated with carboplatin or paclitaxel chemotherapy are mainly available from first-line therapy in ovarian cancer trials. Comparison is relevant, as patients with ovarian cancer are of similar age and have also had previous pelvic surgery, and the combination of radiation and chemotherapy was expected to be more toxic than chemotherapy alone. Ovarian cancer trials with a 3-weekly schema of carboplatin AUC6 and paclitaxel 175–180 mg/mL reported mainly grade 3–4 haematological toxicities, with similar grades of haematological toxicity and febrile neutropenia in the MITO-7 trial³⁰ compared with PORTEC-3, and higher grades reported in the JGOG-3016 trial.³¹ Additionally with this 3-weekly schema, grade 3–4 sensory and motor neuropathy were reported in 6% and 4% respectively in JGOG 3016, compared with 7% and 1% in PORTEC-3, and 3% had any grade 3–4 neuropathy in the MITO-7 trial.

At 24 months after randomisation, patient-reported sensory neuropathy remained significantly worse in the chemoradiotherapy group than in the radiotherapy alone group. A population-based study in ovarian cancer survivors reported peripheral neuropathy (as measured with EORTC-OV28) in 51% of patients treated with chemotherapy versus 27% of participants treated without chemotherapy.³² Neuropathy is a common symptom in the general population, increasing with age and with the prevalence of diabetes.³³ Women with higher levels of neuropathy reported lower levels of functioning and quality of life, and more fatigue.³²

Completion rates for chemotherapy were 93% for cisplatin, 80% for carboplatin, and 72% for paclitaxel, with dose reductions in 7% of carboplatin and 10% of paclitaxel cycles. Completion was lower than in RTOG9708,¹⁶ but reflects clinical practice in a large multicentre trial. In MITO-7,³⁰ 90% of the patients treated carboplatin-paclitaxel received all six cycles; but with dose reductions in 36%. No significant differences were seen between the treatment groups in sexual functioning. Similar to health-related quality of life findings in the PORTEC-1 and PORTEC-2 trials, baseline sexual activity just after surgery and during treatment was low, with improvement over time, but sexual activity in this elderly patient group remained lower compared with population data.⁶

The current endometrial cancer module (EN24) was not yet available when the PORTEC-3 trial was designed. Therefore the CX24 module has been used with the subscale of chemotherapy from OV28, which has not been specifically tested for endometrial cancer. This could be a possible limitation to the study, although the EN24 module is very similar to CX24, with some of the same chemotherapy-related questions as in OV28 included.³⁴ PORTEC-3 assessed both physician-reported and patient-reported toxicities. Limited agreement between patient and physician reported scoring of toxicities has been shown, with significant physician under-reporting of lower grade toxicities.³⁵ In the PORTEC-3 study, physicians were required to report grade 2 or worse adverse events to focus on more severe toxicities, and patient-reported outcomes were used for mild toxicities. Although patient-reported and physician-reported symptoms use different scales, similar trends in types of symptoms over time were seen.

Both the PORTEC-3 trial and the GOG-258 trial used the same combined chemotherapy-radiotherapy schedule, but in comparison with radiotherapy alone and chemotherapy alone, respectively. The toxicity and health-related quality of life outcomes need to be considered in the light of final survival data. If these trials were to show the combined treatment to be superior, future trials should focus on treatment schedules with least toxicity. For ovarian cancer, several trials have been done to compare different (weekly) infusion schedules to achieve a balance between optimum therapy and acceptable toxicity.^{30,31}

Overall, combined adjuvant chemotherapy and radiotherapy for high-risk endometrial cancer caused significantly higher incidence of severe adverse events and reduced

health-related quality of life during and after treatment compared with radiotherapy alone, but with rapid recovery. The most persisting and troublesome symptom was sensory neuropathy, rated as “quite a bit” or “very much” by 25% of patients at 24 months. This schedule of combined chemotherapy and radiotherapy is feasible, and these data are essential for patient counselling and shared decision making on adjuvant chemotherapy. The question remains whether the impact in terms of toxicities will be outweighed by an overall or failure-free survival benefit. Final analysis of the PORTEC-3 and GOG258 trials are awaited, to determine the benefit of chemoradiotherapy in women with high-risk endometrial cancer.

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SUPPLEMENTARY MATERIAL**Table S1.** Questionnaire response rates during follow up

		Questionnaire time point					
		Months					
		Baseline	After RT	6	12	18	24
Responders	Chemoradiotherapy (n)	292	231	215	234	210	194
	Radiotherapy (n)	278	229	218	206	196	170
	Total (n)	570	460	433	440	406	364
Non responders	Missing at baseline (n)	90	90	90	90	90	90
	Response rate (%)	86%	70%	66%	67%	62%	55%

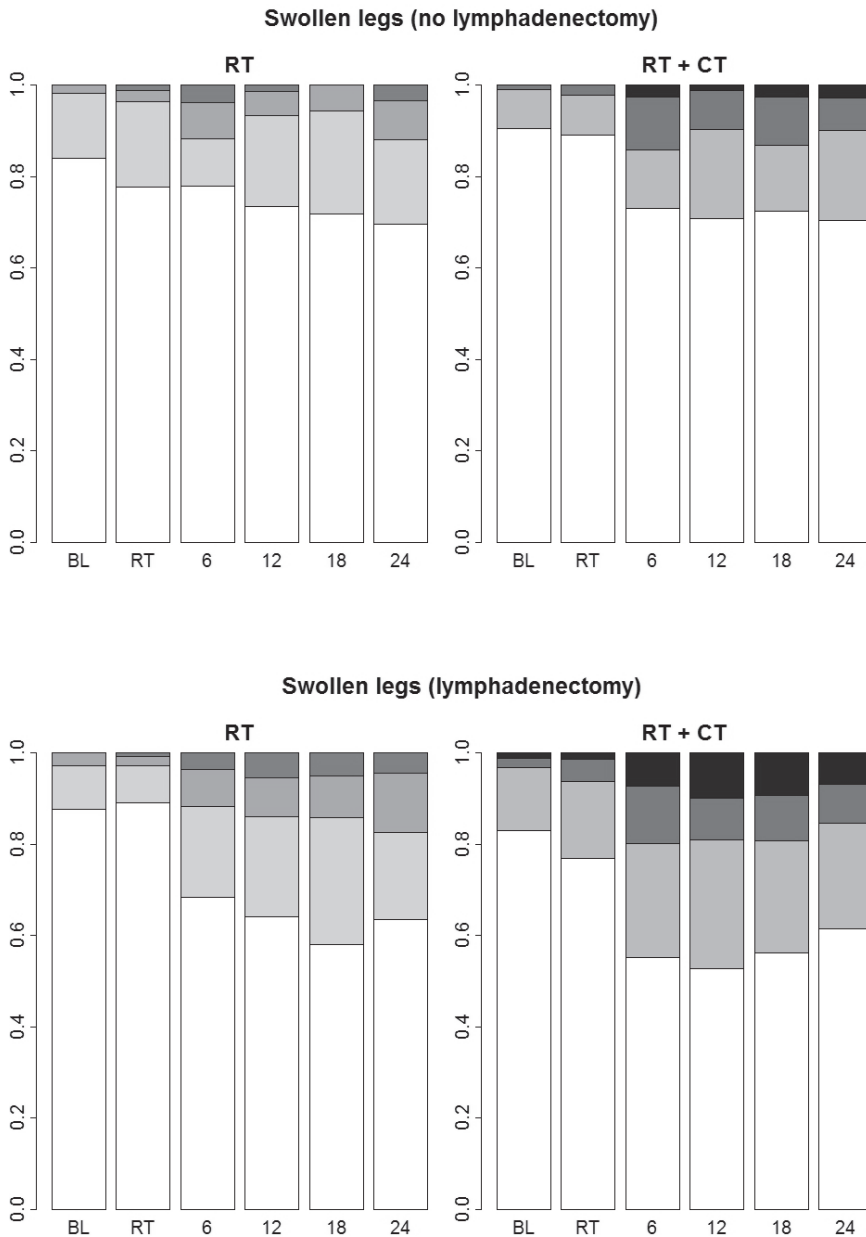


Figure S2. Patient reported swollen legs by lymphadenectomy and by treatment arm. White bar represents % of patients rating the symptom 'not at all', light colour 'a little', more colour 'quite a bit' and darkest colour 'very much'. BL = baseline; RT = at completion of RT (with or without chemotherapy); 6 = 6 months; 12 = 12 months; 18 = 18 months; 24 = 24 months after randomisation. Abbreviations: RT, radiation therapy; CT, combined chemotherapy and radiation therapy.

Table S3. Toxicity reported by physicians using the CTCAE v3.0 during treatment and follow-up.

	Maximum grade per patient during treatment CTRT n=327; RT n=326					
	Grade 2		Grade 3		Grade 4	
	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)
Any	111 (34)	102 (31)	149 (46)	42 (13)	49 (15)	0 (0)
Allergic reaction						
Allergic reaction/ hypersensitivity	23 (7)	1 (0)	5 (2)	0 (0)	1 (0)	0 (0)
Auditory/hearing						
Auditory/hearing	14 (4)	3 (1)	1 (0)	1 (0)	0 (0)	0 (0)
Cardiac (general)						
Edema	7 (2)	2 (1)	1 (0)	0 (0)	0 (0)	0 (0)
Hypertension	19 (6)	12 (4)	6 (2)	3 (1)	0 (0)	0 (0)
Cardiac ischemia/infarction	1 (0)	0 (0)	1 (0)	0 (0)	1 (0)	0 (0)
Cardiac left ventricular failure	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Cardiovascular general - other	2 (1)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Cardiac arrhythmia	4 (1)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Constitutional symptoms						
Fatigue	70 (21)	7 (2)	10 (3)	0 (0)	0 (0)	0 (0)
Other	28 (9)	2 (1)	1 (0)	0 (0)	2 (1)	0 (0)
Dermatology/skin						
Alopecia	185 (57)	1 (0)	na	na	na	na
Radiation dermatitis	18 (6)	5 (2)	1 (0)	1 (0)	0 (0)	0 (0)
Dermatology, wound complication (non-infectious)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Other	6 (2)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Endocrine						
Pancreatic - glucose intolerance	4 (1)	1 (0)	2 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal						
Any	145 (44)	79 (24)	47 (14)	18 (6)	0 (0)	0 (0)
Anorexia	31 (9)	9 (3)	3 (1)	4 (1)	0 (0)	0 (0)
Constipation	31 (9)	6 (2)	1 (0)	0 (0)	0 (0)	0 (0)
Dehydration	7 (2)	4 (1)	8 (2)	3 (1)	0 (0)	0 (0)
Diarrhea	103 (31)	69 (21)	35 (11)	13 (4)	0 (0)	0 (0)
Fistula	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Ileus/obstruction	3 (1)	5 (2)	2 (1)	2 (1)	0 (0)	0 (0)
Nausea	68 (21)	24 (7)	9 (3)	2 (1)	0 (0)	0 (0)
Proctitis	10 (3)	9 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Stomatitis / pharyngitis	6 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting	31 (9)	9 (3)	5 (2)	0 (0)	0 (0)	0 (0)
Other	22 (7)	5 (2)	2 (1)	0 (0)	0 (0)	0 (0)
Hematological						
Any	99 (30)	19 (6)	108 (33)	18 (6)	40 (12)	0 (0)
Hemoglobin	104 (32)	0 (0)	27 (8)	0 (0)	0 (0)	0 (0)
Leucocytes/ WBC	93 (28)	3 (1)	59 (18)	1 (0)	17 (5)	0 (0)
Lymphocytes	50 (15)	16 (5)	98 (30)	17 (5)	10 (3)	0 (0)
Neutrophils/ granulocytes	60 (18)	1 (0)	38 (12)	1 (0)	28 (9)	0 (0)
Platelets	22 (7)	0 (0)	13 (4)	0 (0)	5 (2)	0 (0)

Table S3. Toxicity reported by physicians using the CTCAE v3.0 during treatment and follow-up. (continued)

	Maximum grade per patient during treatment					
	CTRT n=327; RT n=326					
	Grade 2		Grade 3		Grade 4	
CTRT	RT	CTRT	RT	CTRT	RT	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Infection/ febrile neutropenia						
Febrile neutropenia	na	na	7 (2)	1 (0)	2 (1)	0 (0)
Infection with neutropenia	3 (1)	0 (0)	6 (2)	0 (0)	1 (0)	0 (0)
Infection without neutropenia	21 (6)	1 (0)	10 (3)	0 (0)	2 (1)	0 (0)
Other	11 (3)	3 (1)	2 (1)	0 (0)	0 (0)	0 (0)
Lymphatics						
Lymphatics	7 (2)	4 (1)	2 (1)	0 (0)	0 (0)	0 (0)
Metabolic / laboratory						
Other	14 (4)	1 (0)	7 (2)	1 (0)	3 (1)	0 (0)
Neurology						
Neuropathy - any	78 (24)	1 (0)	21 (6)	0 (0)	2 (1)	0 (0)
Neuropathy - motor	13 (4)	1 (0)	3 (1)	0 (0)	1 (0)	0 (0)
Neuropathy - sensory	75 (23)	0 (0)	20 (6)	0 (0)	2 (1)	0 (0)
Neurology - other	9 (3)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Pain						
Any	101 (31)	23 (7)	31 (9)	4 (1)	0 (0)	0 (0)
Arthralgia	52 (16)	2 (1)	10 (3)	0 (0)	0 (0)	0 (0)
Myalgia	52 (16)	1 (0)	9 (3)	0 (0)	0 (0)	0 (0)
Pelvic/back/bone/extremity/limbs	10 (3)	4 (1)	11 (3)	0 (0)	0 (0)	0 (0)
Head/headache	6 (2)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Neuralgia	2 (1)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Abdomen NOS	14 (4)	9 (3)	4 (1)	4 (1)	0 (0)	0 (0)
Dyspareunia	6 (2)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Dysuria	25 (8)	7 (2)	1 (0)	0 (0)	0 (0)	0 (0)
Other	14 (4)	0 (0)	4 (1)	0 (0)	0 (0)	0 (0)
Pulmonary						
Dyspnae	12 (4)	2 (1)	5 (2)	0 (0)	0 (0)	0 (0)
Other	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal						
Osteonecrosis	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Other	2 (1)	2 (1)	2 (1)	0 (0)	0 (0)	0 (0)
Renal/genitourinary						
Creatinine	7 (2)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Renal failure	na	na	2 (1)	0 (0)	0 (0)	0 (0)
Incontinence	11 (3)	5 (2)	1 (0)	0 (0)	0 (0)	0 (0)
Fistula	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Obstruction	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urinary frequency/ urgency	22 (7)	10 (3)	2 (1)	2 (1)	na	na
Other	4 (1)	3 (1)	1 (0)	1 (0)	0 (0)	0 (0)
Vascular						
Thrombosis/thrombus/embolism	2 (1)	0 (0)	0 (0)	0 (0)	4 (1)	0 (0)

Abbreviations: CTRT, combined chemotherapy and radiotherapy; RT, radiotherapy; GI, gastro-intestinal; GU, genito-urinary; CTCAE v3.0, Common Terminology Criteria for Adverse Events version 3.0; NA, not applicable. Only grade ≥ 2 toxicities had to be reported by physicians. All grade 3 and 4 toxicities are reported, and grade 2 toxicities if occurring in $\geq 10\%$ of patients per time point. There were no grade 5 toxicities. Percentages were rounded to full numbers. AE were calculated at each time point. Per AE, the maximum grade per patient was calculated (worst ever by patient).

Maximum grade per patient at 6 months CTRT n=327; RT n=324						Maximum grade per patient at 12 months CTRT n=305; RT n=304					
Grade 2		Grade 3		Grade 4		Grade 2		Grade 3		Grade 4	
CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)
na	na	0 (0)	0 (0)	0 (0)	0 (0)	na	na	0 (0)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5 (2)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	3 (1)	1 (0)	0 (0)	0 (0)	0 (0)
2 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)
5 (2)	6 (2)	1 (0)	0 (0)	0 (0)	0 (0)	8 (3)	3 (1)	2 (1)	1 (0)	0 (0)	0 (0)
2 (1)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	2 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
42 (13)	1 (0)	6 (2)	2 (1)	2 (1)	0 (0)	26 (9)	2 (1)	4 (1)	1 (0)	0 (0)	0 (0)
7 (2)	1 (0)	2 (1)	2 (1)	1 (0)	0 (0)	1 (0)	0 (0)	3 (1)	1 (0)	0 (0)	0 (0)
42 (13)	0 (0)	4 (1)	0 (0)	2 (1)	0 (0)	26 (9)	2 (1)	4 (1)	1 (0)	0 (0)	0 (0)
2 (1)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
31 (9)	30 (9)	3 (1)	6 (2)	0 (0)	1 (0)	27 (9)	21 (7)	7 (2)	4 (1)	0 (0)	0 (0)
8 (2)	6 (2)	0 (0)	1 (0)	0 (0)	0 (0)	4 (1)	3 (1)	0 (0)	1 (0)	0 (0)	0 (0)
5 (2)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
10 (3)	8 (2)	0 (0)	3 (1)	0 (0)	0 (0)	12 (4)	5 (2)	3 (1)	1 (0)	0 (0)	0 (0)
2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3 (1)	11 (3)	1 (0)	3 (1)	0 (0)	1 (0)	2 (1)	4 (1)	3 (1)	2 (1)	0 (0)	0 (0)
1 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	5 (2)	4 (1)	1 (0)	0 (0)	0 (0)	0 (0)
4 (1)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)
1 (0)	3 (1)	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	3 (1)	1 (0)	0 (0)	0 (0)	0 (0)
1 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)	2 (1)	2 (1)	0 (0)	1 (0)	0 (0)	0 (0)
1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
na	na	0 (0)	0 (0)	0 (0)	0 (0)	na	na	0 (0)	0 (0)	0 (0)	0 (0)
6 (2)	7 (2)	1 (0)	0 (0)	0 (0)	0 (0)	8 (3)	9 (3)	1 (0)	1 (0)	0 (0)	0 (0)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)
5 (2)	6 (2)	0 (0)	0 (0)	na	na	4 (1)	8 (3)	0 (0)	1 (0)	na	na
1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3 (1)	0 (0)	0 (0)	0 (0)	2 (1)	1 (0)	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)

Table S4. Complete overview of percentages of patients reporting 'quite a bit' or 'very much' HRQL symptoms using the EORTC QLQ-C30, CX-24 and subscales of the OV-28.

		Questionnaire time points						p-value		
		Baseline	After RT	Months				Changes over time	Difference between groups	Differences between groups over time
				6	12	18	24			
QLQ-C30 symptoms										
Dyspnoea	CTRT	5.6	9.8	15.5	6.4	11.2	8.5	0.001	0.01	0.25
	RT	2.8	5.2	5.1	5.9	3.6	4.5			
Insomnia	CTRT	24.5	24.7	24.2	17.0	19.3	18.0	0.12	0.59	0.96
	RT	19.5	19.0	19.1	13.9	17.1	12.5			
Appetite loss	CTRT	6.6	23.9	10.7	2.6	1.9	2.1	<0.001	0.01	0.02
	RT	4.5	16.4	4.7	5.4	4.1	4.0			
Constipation	CTRT	10.8	4.7	8.0	3.8	6.3	4.7	0.009	0.03	0.10
	RT	7.0	1.3	1.9	4.9	2.6	3.4			
Diarrhoea	CTRT	5.6	36.2	13.2	9.8	9.2	10.0	<0.001	0.96	0.92
	RT	3.8	35.9	12.6	11.2	8.4	11.5			
Financial difficulties	CTRT	12.2	10.7	16.0	8.5	7.3	6.3	<0.001	0.07	0.30
	RT	7.7	7.5	7.0	3.0	4.7	4.6			
CX-24										
Bowel symptoms										
1. Abdominal cramps	CTRT	6.3	17.2	9.8	9.4	6.8	10.1	<0.001	0.85	0.82
	RT	5.0	15.5	8.5	11.3	7.9	7.5			
1. Difficulty controlling bowels	CTRT	2.8	20.5	9.4	8.9	9.2	7.4	<0.001	0.48	0.37
	RT	1.4	20.7	11.8	10.0	7.9	12.2			
1. Blood in the stool	CTRT	0.7	1.3	0.9	0.0	0.5	1.6	0.89	0.90	0.90
	RT	0.4	0.4	1.4	0.5	0.0	0.6			
Urinary symptoms										
1. Urinary frequency	CTRT	23.2	37.8	21.0	21.0	19.9	18.6	<0.001	0.63	0.51
	RT	22.0	37.5	17.4	24.5	17.1	23.1			
1. Dysuria	CTRT	5.2	16.7	1.4	2.6	3.9	2.1	<0.001	0.59	0.46
	RT	4.2	14.2	3.8	3.4	3.7	1.7			
1. Urinary leakage	CTRT	2.8	6.4	7.9	6.8	14.1	9.5	<0.001	0.06	0.05
	RT	4.2	4.3	4.7	9.3	7.3	10.9			
1. Difficulty emptying the bladder	CTRT	4.2	4.7	1.9	1.7	3.4	2.1	0.15	0.70	0.58
	RT	2.8	4.8	2.8	3.5	3.1	3.4			
Other										
Swollen legs	CTRT	2.4	4.7	17.8	15.8	17.0	13.3	<0.001	0.20	0.45
	RT	2.5	3.0	11.7	11.3	11.1	15.5			

Table S4. Complete overview of percentages of patients reporting 'quite a bit' or 'very much' HRQL symptoms using the EORTC QLQ-C30, CX-24 and subscales of the OV-28. (continued)

		Questionnaire time points						p-value		
		Baseline	After RT	Months				Changes over time	Difference between groups	Differences between groups over time
				6	12	18	24			
1. Lower back pain	CTRT	10.8	10.3	15.8	18.4	20.2	18.9	<0.001	0.93	0.89
	RT	8.8	7.8	16.5	15.1	16.9	17.7			
Tingling/numbness	CTRT	1.7	6.1	51.9	33.6	24.2	25.3	<0.001	<0.001	<0.001
	RT	1.4	2.6	7.2	10.4	6.3	6.3			
1. Irritation/soreness vagina/vulva	CTRT	2.8	8.2	4.7	3.4	1.5	1.6	0.002	0.23	0.22
	RT	1.4	11.3	3.8	5.9	4.7	3.4			
1. Vaginal discharge	CTRT	2.8	2.2	2.3	2.1	1.9	0.5	0.78	0.52	0.44
	RT	1.4	4.3	1.4	1.5	0.5	0.6			
1. Vaginal bleeding (abnormal)	CTRT	0.7	0.9	1.9	1.3	0.5	0.0	0.78	0.93	0.93
	RT	1.0	0.4	0.9	0.5	0.5	0.0			
Hot flushes and/or sweats	CTRT	16.3	14.1	19.2	17.9	16.6	15.2	0.35	0.18	0.12
	RT	12.6	15.6	23.9	23.0	17.9	21.4			
2. Feeling of physically less attractive	CTRT	0.5	13.3	24.8	10.2	8.3	8.4	<0.001	<0.001	0.21
	RT	0.3	6.9	7.5	5.9	5.3	5.2			
2. Feeling of less feminine	CTRT	4.9	8.2	16.7	10.2	7.8	8.9	<0.001	0.04	0.38
	RT	3.5	7.0	6.6	6.8	4.7	5.7			
2. Dissatisfied with body	CTRT	5.6	9.0	17.5	13.1	12.7	12.6	<0.001	0.27	0.50
	RT	3.9	8.8	9.4	10.3	8.4	7.6			
Sexual functioning										
Worries about sex	CTRT	13.0	20.1	17.6	15.8	15.0	12.5	0.06	0.89	0.81
	RT	14.3	19.2	15.3	14.1	11.4	16.0			
Sexual activity [†]	CTRT	98.1	99.1	96.7	93.8	90.3	94.0	<0.001	0.01	0.006
	RT	98.1	95.4	89.3	90.2	93.6	93.2			
3. Vaginal dryness*	CTRT	10.0	19.6	20.6	27.4	18.8	23.2	0.24	0.36	0.27
	RT	2.1	25.5	21.1	23.3	28.0	32.2			
3. Shortness of vagina*	CTRT	4.2	8.9	7.9	15.3	14.3	24.1	0.12	0.92	0.85
	RT	2.1	10.9	14.1	19.1	16.0	22.8			
3. Tightness of vagina*	CTRT	6.4	28.3	18.2	16.7	18.8	16.4	0.06	0.12	0.07
	RT	4.2	14.8	21.3	21.3	17.3	27.1			
3. Pain during sexual intercourse*	CTRT	0.0	23.8	12.9	9.9	8.7	12.5	0.25	0.35	0.36
	RT	2.3	20.0	17.0	21.1	18.7	26.7			
Sexual activity enjoyable?*	CTRT	63.0	81.6	62.9	60.3	69.1	60.0	0.03	0.01	0.01
	RT	69.0	54.5	57.6	52.2	52.1	62.7			

Table S4. Complete overview of percentages of patients reporting 'quite a bit' or 'very much' HRQL symptoms using the EORTC QLQ-C30, CX-24 and subscales of the OV-28. (continued)

		Questionnaire time points						p-value		
		Baseline	After RT	Months				Changes over time	Difference between groups	Differences between groups over time
				6	12	18	24			
OV 28										
Bloated feeling abdomen/stomach	CTRTRT	12.6	15.3	18.4	9.4	9.7	11.1	0.03	0.18	0.13
	RT	11.2	14.8	14.4	16.2	13.6	11.6			
Passing wind/ gas/ flatulence	CTRTRT	16.7	21.0	23.0	19.7	21.2	23.7	0.34	0.33	0.34
	RT	11.4	18.7	21.1	22.1	22.0	18.2			
4. Loss of any hair	CTRTRT	1.4	10.8	44.0	4.8	4.5	0.5	<0.001	<0.001	<0.001
	RT	0.4	3.5	3.8	3.9	3.1	2.3			
4. Upset by loss of hair**	CTRTRT	3.3	25.3	41.2	30.0	26.5	12.9	0.05	0.10	0.24
	RT	5.0	3.7	14.3	13.0	7.5	8.3			
4. Different taste of food and drink	CTRTRT	3.6	27.0	21.7	4.0	4.5	2.2	<0.001	<0.001	0.03
	RT	0.7	9.8	4.8	3.1	2.7	2.3			
5. Tingling hand/ feet	CTRTRT	1.1	6.9	49.1	25.8	22.2	23.7	<0.001	<0.001	<0.001
	RT	1.8	2.2	6.3	5.6	4.8	5.3			
5. Numbness fingers/ toes	CTRTRT	1.4	5.2	49.5	27.8	25.1	25.3	<0.001	<0.001	<0.001
	RT	0.4	2.7	5.3	4.1	3.7	4.1			
5. Weakness arms/ legs	CTRTRT	6.1	13.5	35.5	16.1	17.1	14.3	<0.001	<0.001	0.16
	RT	2.9	6.7	11.5	7.2	5.9	6.9			
4. Muscle or joint pain	CTRTRT	9.7	16.3	37.4	24.0	23.8	24.3	<0.001	0.05	0.10
	RT	7.0	13.5	21.7	19.3	23.5	19.1			
4. Problems hearing	CTRTRT	2.5	3.0	10.8	6.5	8.9	7.4	<0.001	0.39	0.52
	RT	2.2	1.8	4.9	6.6	4.3	4.6			

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire C30; CTRTRT, combined chemotherapy and radiotherapy; RT, radiotherapy; CX, cervix; OV, ovarian; HRQL, health-related quality of life; Tx, treatment. P time: changes of quality-of-life scores over time. P Tx: difference in health-related quality of life between the two treatment groups. P time by Tx: the difference in health-related quality of life between the two treatment groups over time. # this percentage reflects patients who indicated to be not or just a little bit sexually active. * responses to these questions were only expected if the respondent indicated to be sexually active. ** responses to this question was only expected if the respondent indicated to have loss of hair. 1. Symptom experience subscale; 2. Body image subscale; 3. Sexual functioning subscale; 4. Chemotherapy subscale; 5. Peripheral neuropathy subscale.

