Universiteit Leiden
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# Towards personalized treatment for high risk endometrial cancer

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# Chapter 2

## Long-term toxicity and health-related quality of life after adjuvant chemoradiotherapy or radiotherapy alone for high risk endometrial cancer in the randomized PORTEC-3 trial

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# ABSTRACT

## Purpose

The survival results of the PORTEC-3 trial showed a significant improvement in both overall and failure-free survival with chemoradiotherapy versus pelvic radiotherapy alone. The present analysis was performed to compare long-term adverse events (AE) and health-related quality of life (HRQOL).

## Methods and materials

In the study, 660 women with high risk endometrial cancer were randomly assigned to receive chemoradiotherapy (2 concurrent cycles of cisplatin followed by 4 cycles of carboplatin/paclitaxel) or radiotherapy alone. Toxicity was graded using Common Terminology Criteria for Adverse Events, version 3.0. HRQOL was measured using EORTC QLQ-C30 and CX24/OV28 subscales and compared with normative data. An as-treated analysis was performed.

## Results

Median follow-up was 74.6 months; 574 (87%) patients were evaluable for HRQOL. At 5 years, grade ≥2 AE were scored for 78 (38%) patients who had received chemoradiotherapy versus 46 (24%) who had received radiotherapy alone ($p$ = .008). Grade 3 AE did not differ significantly between the groups (8% vs 5%; $p$ = .18) at 5 years, and only one new late grade 4 toxicity had been reported. At 3 and 5 years, sensory neuropathy toxicity grade ≥2 persisted after chemoradiotherapy in 6% (vs 0% after radiotherapy; $p$ < .001) and more patients reported significant tingling or numbness at HRQOL (27% vs 8%, $p$ < .001 at 3 years; 24% vs 9%, $p$ = .002 at 5 years). Up to 3 years, more patients who had chemoradiotherapy reported limb weakness (21% vs 5%; $p$ < .001) and lower physical (79 vs 87; $p$ < .001) and role functioning (78 vs 88; $p$ < .001) scores. Both treatment groups reported similar long-term global health/quality of life scores, which were better than those of the normative population.

## Conclusions

This study shows a long-lasting, clinically relevant, negative impact of chemoradiotherapy on toxicity and HRQOL, most importantly persistent peripheral sensory neuropathy. Physical and role functioning impairments were seen until 3 years. These long-term data are essential for patient information and shared decision-making regarding adjuvant chemotherapy for high risk endometrial cancer.






# Introduction

The majority of endometrial cancers are diagnosed at an early stage, but 15% to 20% of women with endometrial cancer present with high risk disease. These high risk cancers are characterized by higher grade, advanced stage, or non-endometrioid histology. In contrast to the favorable prognosis of most early-stage endometrial cancers, the high risk group has an increased incidence of distant metastases and cancer-related death. Adjuvant pelvic radiotherapy has been the standard of care for these patients to maximize locoregional control;[1] however, chemotherapy could reduce distant metastases.

The randomized PORTEC-3 trial was initiated to evaluate the benefit of combined adjuvant pelvic radiotherapy and chemotherapy versus pelvic radiotherapy alone for women with high risk endometrial cancer. The updated survival analysis of the PORTEC-3 trial showed a significant benefit in 5-year overall survival and failure-free survival with absolute improvement of, respectively, 5% (81% vs 76%, hazard ratio [HR] 0.70; $p$ = .034) and 7% (76% vs 69%, HR 0.70; $p$ = .016) after chemoradiotherapy. Patients with serous cancers and those with stage III disease were shown to benefit most from the addition of chemotherapy (absolute overall survival improvement of 19% and 10%, respectively, and failure-free survival improvement of 12% and 13%).[2] For each individual patient, the potential survival benefit of chemotherapy should be weighed against the costs of longer treatment duration, increased toxicity, and influence on health-related quality of life (HRQOL).

Pelvic radiotherapy is associated with risks of long-term urinary urgency and incontinence, and bowel symptoms such as diarrhea and fecal leakage, as well as lower physical and role functioning.[3,4] In the analysis of short-term toxicity and HRQOL in the PORTEC-3 trial, the addition of chemotherapy was shown to worsen the toxicity profile with more severe adverse events (AE) and impaired HRQOL during and after chemoradiotherapy. However, rapid recovery was seen; from 12 months onward there was no between-group difference in grade 3 to 4 toxicity, and grade 2 or higher sensory neuropathy was the main persistent AE at 24 months in 10% after chemoradiotherapy.[5] Several studies have reported a negative correlation between chemotherapy-induced peripheral neuropathy (CIPN) and physical functioning or HRQOL.[6-11]

The present analysis was performed to establish long-term AE and patient-reported HRQOL for up to 5-year follow-up in women with high risk endometrial cancer treated in the PORTEC-3 trial. The secondary objective was to evaluate whether specific conditions are correlated to HRQOL.

# Methods and materials

## Patient population and study design

Details of this open-label, multicenter, randomized phase 3 trial have been reported previously.[2,5,12] Briefly, patients were enrolled at 103 centers through 6 clinical trial groups. Patients were eligible if they had high risk endometrial cancer, defined as histologically confirmed International Federation of Gynecology and Obstetrics (FIGO) 2009 stage I endometrioid endometrial cancer grade 3 with myometrial invasion or lymph-vascular space invasion; stage II or III endometrioid endometrial cancer; or stage I to III serous or clear-cell histology. Surgery consisted of hysterectomy with bilateral salpingo-oophorectomy; clinically suspicious pelvic or periaortic lymph nodes were removed, but lymphadenectomy was not mandatory. Patients were randomly assigned (1:1) to receive pelvic radiotherapy (48.6 Gy in 1.8 Gy fractions, with a brachytherapy boost in case of cervical stromal involvement) or chemoradiotherapy (2 cycles of cisplatin 50 mg/m2 in weeks 1 and 4 of radiotherapy, followed by 4 cycles of carboplatin AUC5 and paclitaxel 175 mg/m2 at 3-week intervals). The study was approved by the Dutch Cancer Society and ethics committees of participating groups.

## Study outcome measures

A prespecified secondary objective of the PORTEC-3 trial was to assess AE (grade ≥2 irrespective of study treatment, according to Common Terminology Criteria for Adverse Events [CTCAE] version 3.0) and for mild toxicities (grade 1) HRQOL using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), the cervix 24 (CX24) module, and added neuropathy subscale and other chemotherapy side effect subscale items from the ovarian 28 (OV28) module.[13,14] These were used because the EORTC endometrial module was not yet available at the time of study design. HRQOL questionnaires were completed at baseline (after surgery), after radiotherapy, and at 6, 12, 18, 24, 36, and 60 months from randomization and were discontinued upon diagnosis of recurrence or death. For all items, Likert-type response scales were used ranging from 4 to 7 points. Higher scores on functional and global HRQOL scales represented better levels of functioning. Higher scores on symptom subscales reflected higher levels of symptoms.

## Statistical analysis

We used $X^2$ statistics or the Fisher exact test for categorical variables and the *t* test or Mann-Whitney *U* test for continuous variables to compare patient and tumor characteristics (significance *p* value <.05). No specific power calculations were done for toxicity and HRQOL analysis. However, the sample size ensured sufficient power to detect clinically relevant differences. Toxicity and HRQOL were analyzed according to treatment received.





The prevalence of toxicity was calculated at each timepoint (using the maximum grade scored) and compared between the 2 treatment groups by the Fisher exact test.

Patients who completed baseline and at least 1 follow-up questionnaire were evaluable for HRQOL analysis. Missing data were handled as missing at random. As in previous analysis, a prespecified HRQOL analysis was done according to the EORTC Quality of Life Group guidelines.[5,15] A linear mixed model was used to obtain estimates for 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 as fixed effects. Single items were analyzed with generalized mixed models (binary) logistic regression with the same random and fixed effects as in the linear mixed model, combining scores of 1 to 2 ("not at all" and "a little") and 3 to 4 ("quite a bit" and "very much"). Additional linear mixed models were used within treatment arms with time, age, and their interaction as fixed effects. The difference in HRQOL 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. Age-matched normative population means[16,17] were compared with both treatment groups using the *t* test. General population normative data of more than 1500 women across Europe and North America aged 60 to 69 years[16] were used for the EORTC QLQ-C30 scales, and general Dutch population normative data of 87 women aged 61 to 70 years were used for sexuality items.[17]

Guidelines on the interpretation of clinically relevant between-group differences in EORTC QLQ-C30 scores were applied (trivial, small, medium, or large differences per scale).[18] An additional post hoc analysis was performed to assess long-term (3-year and 5-year mean) changes from baseline at individual level. Between-group differences on scales not included in the guidelines and long-term changes were assessed according to Osoba et al.[19] Improvement and deterioration were defined respectively as a ≥10-point increase or decrease, and a stable score was defined as a <10-point change. Changes were compared between treatment groups using the Fisher exact test. In addition, Kendall's rank correlation was used post hoc to measure the ordinal association between different HRQOL items and scales. Finally, stepwise binary logistic regression with likelihood ratio test–based backward selection was performed to identify risk factors for developing tingling/numbness, including diabetes, cardiovascular disease, hypertension, age (≥70 years), type of surgery, performance status, and chemotherapy compliance.

To guard against false-positive results due to multiple testing, a 2-sided *p* value ≤.01 was considered statistically significant, and *p* values <.05 were reported as a trend. Statistical analyses were done with SPSS, version 25, and R, version 3.6.1.

# Results

## Study population and compliance

The PORTEC-3 trial accrued 660 eligible patients between 2006 and 2013; 333 patients received radiotherapy alone and 327 patients received chemoradiotherapy. At the time of analysis, median follow-up was 74.6 months (interquartile range, 60-86). Patient and treatment characteristics were well balanced between the groups (Table 1).

Baseline questionnaires and at least 1 follow-up questionnaire were received from 574 (87%) patients (292 in the chemoradiotherapy group and 282 in the radiotherapy-alone group). At 3 years, the completion rate was 89%, and at 5 years it was 63% (Appendix Table A1). Age distribution remained constant over time (data not shown). World Health Organization performance score differed between responders and nonresponders at baseline, with a score of ≥2 in 5 (1%) of the 574 responders versus 5 (6%) of the 86 non-responders ($p$ = .005, Appendix Table A3). At baseline, 88% of the responders had completed all items of the EORTC QLQ-C30, 83% all items of the CX24 subscales, 95% all nonsexual items, and 91% all items of the OV28 subscale.

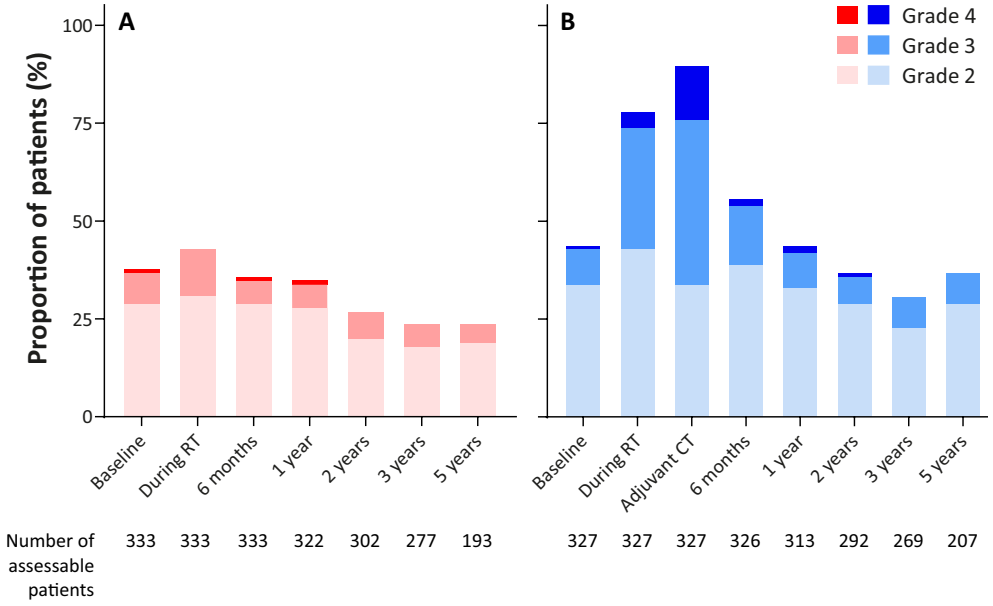


**Figure 1.** Incidence of the maximum physician-reported adverse event grades per patient for each timepoint at baseline, during treatment, at 6 months follow-up and at, 1, 2, 3 and 5 years follow-up after pelvic radiotherapy alone (A) and combined pelvic radiotherapy and chemotherapy (B).
CT = chemotherapy; RT = radiotherapy.



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

| | **Chemoradiotherapy** | **Radiotherapy alone** |
|---|---|---|
| | ***n* = 327** | ***n* = 333** |
| **Age at randomization (y)** | | |
| Median | 61.9 (55.9 - 68.1) | 62.5 (56.5 - 68.0) |
| <60 | 127 (39%) | 141 (42%) |
| 60-69 | 142 (43%) | 130 (39%) |
| ≥70 | 58 (18%) | 62 (19%) |
| **WHO performance score** | | |
| 0-1 | 320 (98%) | 327 (98%) |
| 2 | 5 (2%) | 5 (2%) |
| **Comorbidities** | | |
| Diabetes | 45 (14%) | 36 (11%) |
| Hypertension | 115 (35%) | 105 (32%) |
| Cardiovascular | 29 ( 9%) | 20 ( 6%) |
| **FIGO 2009 stage** | | |
| Ia | 39 (12%) | 39 (12%) |
| Ib | 58 (18%) | 59 (18%) |
| II | 79 (24%) | 91 (27%) |
| III | 151 (46%) | 144 (43%) |
| **Type of surgery** | | |
| TAH-BSO | 94 (29%) | 97 (29%) |
| TAH-BSO with LND or full staging | 142 (44%) | 134 (40%) |
| TLH-BSO | 44 (13%) | 44 (13%) |
| TLH-BSO with LND or full staging | 47 (14%) | 58 (17%) |
| **Treatment completion** | | |
| RT completion | 326 (100%) | 328 (98%) |
| Brachytherapy boost | 149 (46%) | 160 (48%) |
| 1 cycle cisplatin | 325 (99%) | 0 |
| 2 cycles cisplatin | 304 (93%) | 0 |
| 1 cycle carboplatin/paclitaxel | 303 (93%)/303 (93%) | 0 |
| 2 cycles carboplatin/paclitaxel | 295 (90%)/295 (90%) | 0 |
| 3 cycles carboplatin/paclitaxel | 279 (85%)/266 (82%) | 0 |
| 4 cycles carboplatin/paclitaxel | 262 (80%)/235(72%) | 0 |

Data are median (IQR) or *n* (%). FIGO = International Federation of Gynaecology and Obstetrics; TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy; LND = lymph node dissection; TLH = total laparoscopic hysterectomy; RT = radiotherapy.

## Adverse events

AE reported over time are summarized in Table 2 and Figure 1. At baseline (after surgery), no significant between-group differences were found; grade ≥2 baseline AE were scored for 143 (44%) patients in the chemoradiotherapy group and 124 (37%) patients in the radiotherapy group. The most frequently scored AE was hypertension (27%). At 5 years, grade ≥2 AE were reported for 78 (38%) patients who had received chemoradiotherapy versus 46 (24%) patients who had received radiotherapy ($p$ = .008); grade ≥2 sensory neuropathy persisted in 13 (6%) after chemoradiotherapy versus none after radiotherapy alone ($p$ < .001). Other grade ≥2 AE did not significantly differ between groups at 5 years, including hypertension in 10% and urinary incontinence in 5% in both groups. Urinary urgency was reported in 9 (4%) versus 3 (2%) patients after chemoradiotherapy versus radiotherapy; any gastrointestinal toxicity in 17 (8%) versus 11 (6%), including diarrhea in 9 (4%) versus 7 (3%) and pain in 18 (9%) versus 9 (5%); and most often arthralgia in 11 (5%) versus 5 (3%). Grade 3 AE did not differ significantly between the groups at 5 years (5% vs 8%; $p$ = .18), and only 1 new grade 4 AE was reported (ileus/obstruction requiring surgery 5 years after chemoradiotherapy).

## HRQOL subscales

Results of the EORTC QLQ-C30 functioning and global health/quality of life (QOL) subscales and CX24 and OV28 subscales are summarized in Table 3. Up to 3 years, small clinically relevant differences were found for physical and role functioning (Figure 2A, 2B). At 3 years, mean scores were 79 versus 87 ($p$ < .001) for physical functioning and 78 versus 88 ($p$ < .001) for role functioning after chemoradiotherapy and radiotherapy, respectively; these scores were trivially different from the age-matched normative population. Long-term global health/QOL scores were not statistically or clinically different between the treatment groups. However, small to medium clinically relevant better scores were seen in the PORTEC-3 study population compared with the normative population (Figure 2C). Trends for worse long-term pain and fatigue symptom scores after chemoradiotherapy were seen, with the largest difference at 3 years (20.5 vs 14.1, $p$ = .008; 26.0 vs 20.7, $p$ = .015, respectively); these were small but clinically relevant differences. No long-term significant differences in social, cognitive, and emotional functioning were found between treatment groups or in comparison to the normative population (Appendix Figure A1, A2).

Among patients who had received chemoradiotherapy, age groups (<70 vs ≥70 years) differed in their change in scores over time for physical functioning ($p$ < .001), role functioning ($p$ = .011), global health/QOL ($p$ < .001), pain ($p$ = .004), and fatigue ($p$ = .002); being more unfavorable in older patients. This also applies within the radiotherapy group for the physical and role functioning scores ($p$ < .01), although not for global health/QOL ($p$ = .42), pain ($p$ = .33), and fatigue ($p$ = .19). Data are displayed in Appendix Figure A3.





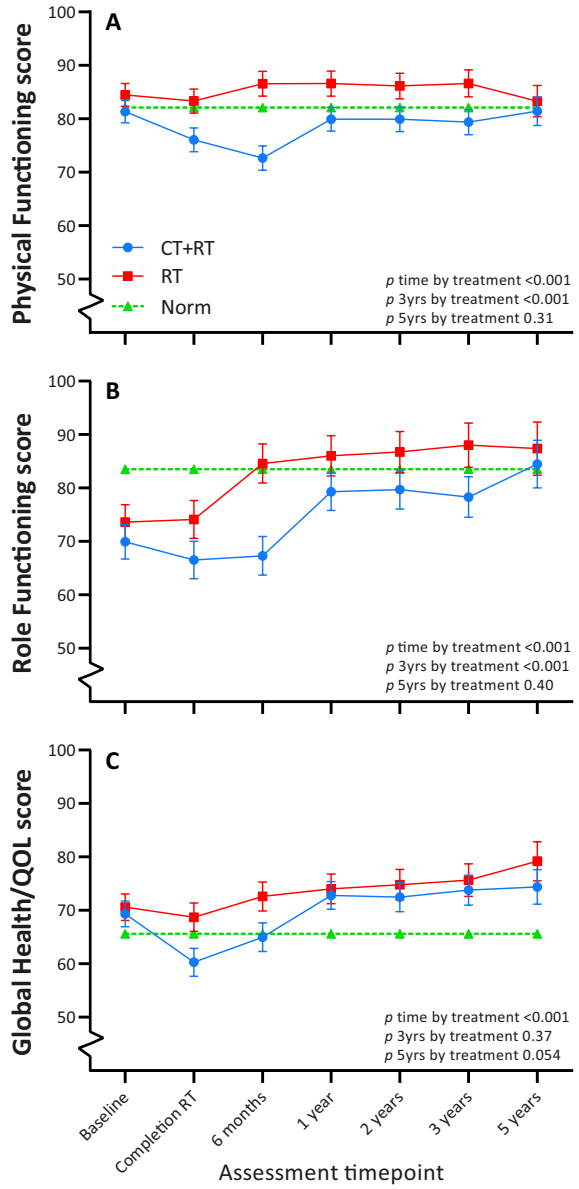


**Figure 2.** Patient functioning on subscales from EORTC QLQ-C30 for physical functioning (A), role functioning (B), global health status/quality of life (C).

A higher score indicates a higher level of functioning or activity. Error bars show 95% CI. EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; $p$ time by treatment = difference between the two treatment groups over time; $p$ 3yrs by treatment = difference between the two treatment groups at 3 years; $p$ 5yrs by treatment = difference between the two treatment groups at 5 years; CT = chemotherapy; Norm = mean scores of age-match normative data based on women aged 60-69 years across 13 European countries, Canada and the United States;[16] RT = radiotherapy.

**Table 2.** Adverse events reported by physicians using Common Terminology Criteria for Adverse Events version 3.0 during treatment and at 3 and 5 years follow-up.

| | Maximum grade per patient during treatment CTRT *n* = 327; RT *n* = 333 | | | | | | Maximum grade per patient at 3 years CTRT *n* = 269; RT *n* = 277 | | | | | | Maximum grade per patient at 5 years CTRT *n* = 207; RT *n* = 193 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Grade 2** | | | **Grade 3/4** | | | **Grade 2** | | | **Grade 3/4** | | | **Grade 2** | | | **Grade 3/4** | | |
| | **CTRT** | **RT** | ***p**** | **CTRT** | **RT** | ***p#*** | **CTRT** | **RT** | ***p**** | **CTRT** | **RT** | ***p#*** | **CTRT** | **RT** | ***p**** | **CTRT** | **RT** | ***p#*** |
| | ***n* (%)** | ***n* (%)** | | ***n* (%)** | ***n* (%)** | | ***n* (%)** | ***n* (%)** | | ***n* (%)** | ***n* (%)** | | ***n* (%)** | ***n* (%)** | | ***n* (%)** | ***n* (%)** | |
| **Any** | 110 (34) | 103 (31) | <0.01 | 198 (61) | 41 (12) | <0.01 | 63 (23) | 49 (18) | 0.04 | 21(8) | 16 (6) | 0.40 | 60 (29) | 37 (19) | <0.01 | 18 (9) | 9 (5) | 0.18 |
| **Any grade 3** | na | na | | 148 (45) | 41 (12) | | na | na | | 20 (7) | 16 (6) | | na | na | | 17 (8) | 9 (5) | |
| **Any grade 4** | na | na | | 50 (15) | 0 (0) | | na | na | | 1 (0) | 0 (0) | | na | na | | 1 (0) | 0 (0) | |
| Auditory/hearing | 14 (4) | 3 (1) | <0.01 | 1 (0) | 1 (0) | 1.00 | 1 (0) | 1 (0) | 1.00 | 1 (0) | 1 (0) | 1.00 | 4 (2) | 1 (1) | 0.29 | 2 (1) | 1 (1) | 1.00 |
| Hypertension | 19 (6) | 12 (4) | 0.10 | 6 (2) | 3 (1) | 0.34 | 15 (6) | 17 (6) | 0.75 | 5 (2) | 6 (2) | 1.00 | 16 (8) | 17 (9) | 0.63 | 4 (2) | 5 (3) | 0.74 |
| Lymphatics (edema) | 7 (2) | 4 (1) | 0.17 | 2 (1) | 0 (0) | 0.25 | 3 (1) | 1 (0) | 0.12 | 2 (1) | 0 (0) | 0.24 | 5 (2) | 2 (1) | 0.45 | 0 (0) | 0 (0) | 1.00 |
| **Gastrointestinal - any** | 145 (44) | 79 (24) | <0.01 | 47 (14) | 18 (5) | <0.01 | 11 (4) | 17 (6) | 0.46 | 2 (1) | 1 (0) | 0.62 | 15 (7) | 10 (5) | 0.43 | 2 (1) | 1 (1) | 1.00 |
| Diarrhea | 103 (31) | 68 (20) | <0.01 | 35 (11) | 14 (4) | <0.01 | 4 (1) | 8 (3) | 0.42 | 1 (0) | 1 (0) | 1.00 | 7 (3) | 7 (4) | 0.80 | 2 (1) | 0 (0) | 0.50 |
| Ileus/obstruction | 3 (1) | 5 (2) | 0.77 | 2 (1) | 2 (1) | 1.00 | 0 (0) | 0 (0) | 0.49 | 1 (0) | 0 (0) | 0.49 | 2 (1) | 1 (1) | 0.22 | 3 (1) | 0 (0) | 0.25 |
| **Hematological - any** | 100 (31) | 19 (6) | <0.01 | 149 (46) | 18 (5) | <0.01 | 3 (1) | 3 (1) | 1.00 | 1 (0) | 2 (1) | 1.00 | 5 (2) | 5 (3) | 1.00 | 0 (0) | 0 (0) | 1.00 |
| Lymphocytes | 48 (15) | 16 (5) | <0.01 | 109 (33) | 17 (5) | <0.01 | 1 (0) | 0 (0) | 0.49 | 0 (0) | 0 (0) | 1.00 | 3 (1) | 4 (2) | 0.72 | 0 (0) | 0 (0) | 1.00 |
| **Neuropathy - any** | 82 (25) | 1 (0) | <0.01 | 23 (7) | 0 (0) | <0.01 | 18 (7) | 2 (1) | <0.01 | 2 (1) | 0 (0) | 0.24 | 13 (6) | 0 (0) | <0.01 | 1 (0) | 0 (0) | 1.00 |
| Neuropathy - motor | 13 (4) | 1 (0) | <0.01 | 4 (1) | 0 (0) | 0.06 | 3 (1) | 2 (1) | 0.44 | 1 (0) | 0 (0) | 0.49 | 1 (0) | 0 (0) | 0.50 | 1 (0) | 0 (0) | 1.00 |
| Neuropathy - sensory | 79 (24) | 0 (0) | <0.01 | 22 (7) | 0 (0) | <0.01 | 18 (7) | 1 (0) | <0.01 | 2 (1) | 0 (0) | 0.24 | 12 (6) | 0 (0) | <0.01 | 1 (0) | 0 (0) | 1.00 |
| **Pain - any** | 101 (31) | 23 (7) | <0.01 | 31 (9) | 4 (1) | <0.01 | 17 (6) | 15 (5) | 0.30 | 4 (1) | 0 (0) | 0.06 | 15 (7) | 6 (3) | 0.12 | 3 (1) | 3 (2) | 1.00 |
| Arthralgia | 52 (16) | 2 (1) | <0.01 | 10 (3) | 0 (0) | <0.01 | 2 (1) | 5 (2) | 0.73 | 1 (0) | 0 (0) | 0.49 | 9 (4) | 4 (2) | 0.20 | 2 (1) | 1 (1) | 1.00 |
| Muscle pain | 52 (16) | 1 (0) | <0.01 | 9 (3) | 0 (0) | <0.01 | 3 (1) | 0 (0) | 0.12 | 0 (0) | 0 (0) | 1.00 | 1 (0) | 1 (1) | 0.61 | 0 (0) | 1 (1) | 0.48 |
| Back/pelvic/limbs | 10 (3) | 4 (1) | <0.01 | 11 (3) | 0 (0) | <0.01 | 4 (1) | 3 (1) | 0.50 | 1 (0) | 0 (0) | 0.49 | 0 (0) | 2 (1) | 0.11 | 0 (0) | 1 (1) | 0.48 |
| Abdomen/cramps | 14 (4) | 9 (3) | 0.28 | 4 (1) | 4 (1) | 1.00 | 5 (2) | 1 (0) | 0.07 | 1 (0) | 0 (0) | 0.49 | 2 (1) | 0 (0) | 0.12 | 2 (1) | 0 (0) | 0.50 |
| **Musculoskeletal (other)** | 2 (1) | 2 (1) | 0.50 | 2 (1) | 0 (0) | 0.50 | 1 (0) | 0 (0) | 0.24 | 1 (0) | 0 (0) | 0.49 | 0 (0) | 1 (1) | 1.00 | 0 (0) | 0 (0) | 1.00 |
| Pulmonary - dyspnea | 14 (4) | 2 (1) | 0.25 | 5 (2) | 0 (0) | 0.03 | 1 (0) | 0 (0) | 1.00 | 0 (0) | 1 (0) | 1.00 | 2 (1) | 0 (0) | 0.50 | 0 (0) | 0 (0) | 1.00 |
| **Genitourinary** | | | | | | | | | | | | | | | | | | |
| Incontinence | 12 (4) | 5 (2) | 0.06 | 1 (0) | 0 (0) | 0.50 | 8 (3) | 3 (1) | 0.09 | 1 (0) | 0 (0) | 0.49 | 8 (4) | 9 (5) | 1.00 | 0 (0) | 0 (0) | 1.00 |
| Obstruction | 0 (0) | 1 (0) | 1.00 | 0 (0) | 0 (0) | 1.00 | 0 (0) | 0 (0) | 0.49 | 0 (0) | 1 (0) | 0.49 | 0 (0) | 0 (0) | 1.00 | 0 (0) | 0 (0) | 1.00 |
| Urinary urgency | 24 (7) | 10 (3) | 0.01 | 2 (1) | 2 (1) | 1.00 | 7 (3) | 5 (2) | 0.57 | 0 (0) | 0 (0) | 1.00 | 9 (4) | 3 (2) | 0.14 | 0 (0) | 0 (0) | 1.00 |
| **Constitutional** | | | | | | | | | | | | | | | | | | |
| Fatigue | 69 (21) | 7 (2) | <0.01 | 10 (3) | 0 (0) | <0.01 | 1 (0) | 0 (0) | 0.49 | 0 (0) | 0 (0) | 1.00 | 0 (0) | 3 (2) | 0.11 | 0 (0) | 0 (0) | 1.00 |
| Other | 31 (9) | 2 (1) | <0.01 | 3 (1) | 0 (0) | 0.12 | 1 (0) | 0 (0) | 0.24 | 1 (0) | 0 (0) | 0.49 | 2 (1) | 0 (0) | 0.25 | 1 (0) | 0 (0) | 1.00 |
| **Other toxicity** | 0 (0) | 0 (0) | 1.00 | 0 (0) | 0 (0) | 1.00 | 0 (0) | 1 (0) | 1.00 | 1 (0) | 0 (0) | 0.49 | 2 (1) | 2 (1) | 0.69 | 2 (1) | 0 (0) | 0.50 |

Adverse events were calculated at each timepoint. Per adverse event, the maximum grade per patient was calculated (worst ever by patient). For grade 2, 3, and 4 adverse events, *p* values less than or equal to 0.01 were deemed significant. *p** = significant level < 0.01 for grade ≥2. *p#* = significant level <0.01 for grade 3 and 4.

CTCAE v3.0 = Common Terminology Criteria for Adverse Events version 3.0; CTRT = combined chemotherapy and radiotherapy; RT = radiotherapy.

**Table 3.** Patient reported health-related quality of life using the EORTC QLQ-C30 and subscales of CX-24 and OV-28.

| | | Questionnaire time points | | | | | | *p*-value | | | | | Norm | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Months | | | | | | | | | | |
| | | Baseline | After RT | 6 | 12 | 36 | 60 | Time | Tx | Time by Tx | at 3yr | at 5yr | 60-69 yr | CS |
| **EORTC QLQ C30 functioning scales** | | | | | | | | | | | | | | |
| Physical functioning | CTRT | 81.3 | 76.0 | 72.6 | 79.9 | 79.4 | 81.4 | **<0.001** | **<0.001** | **<0.001** | **<0.001*** | 0.31 | 82.1 | T |
| | RT | 84.5 | 83.3 | 86.5 | 86.6 | 86.6 | 83.5 | | | | | | | T |
| Role functioning | CTRT | 69.9 | 66.5 | 67.3 | 79.3 | 78.3 | 84.5 | **<0.001** | **<0.001** | **<0.001** | **0.0007*** | 0.40 | 83.5 | T |
| | RT | 73.6 | 74.1 | 84.6 | 86.0 | 88.0 | 87.4 | | | | | | | T |
| Emotional functioning | CTRT | 74.4 | 76.9 | 77.0 | 80.7 | 81.6 | 84.6 | **<0.001** | 0.14 | **<0.001** | 0.33 | 0.80 | 77.8 | **S** |
| | RT | 77.4 | 81.5 | 80.8 | 82.7 | 83.5 | 84.0 | | | | | | | **S** |
| Cognitive functioning | CTRT | 86.9 | 81.4 | 79.4 | 83.8 | 83.4 | 86.8 | **<0.001** | **0.0022** | 0.035 | 0.18 | 0.66 | 87.9 | T |
| | RT | 87.9 | 85.8 | 86.9 | 87.3 | 86.4 | 87.8 | | | | | | | T |
| Social functioning | CTRT | 77.7 | 73.5 | 74.0 | 84.2 | 85.4 | 90.2 | **<0.001** | **<0.001** | **<0.001** | 0.43 | 0.72 | 88.1 | T |
| | RT | 80.1 | 78.7 | 88.1 | 89.9 | 87.2 | 91.2 | | | | | | | T |
| Global health status/ Quality of Life | CTRT | 69.3 | 60.3 | 65.0 | 72.8 | 73.8 | 74.4 | **<0.001** | **<0.001** | **<0.001** | 0.37 | 0.054 | 65.6 | **S** |
| | RT | 70.6 | 68.7 | 72.6 | 74.0 | 75.7 | 79.2 | | | | | | | **M** |
| **QLQ C30 Symptoms scales** | | | | | | | | | | | | | | |
| Fatigue | CTRT | 29.0 | 42.4 | 38.4 | 28.2 | 26.0 | 23.3 | **<0.001** | **<0.001** | **<0.001** | 0.015 | 0.058 | 26.6 | T |
| | RT | 26.6 | 34.4 | 23.8 | 22.8 | 20.7 | 18.4 | | | | | | | **S** |
| Nausea and vomiting | CTRT | 3.7 | 14.1 | 9.1 | 5.1 | 3.7 | 4.2 | **<0.001** | **<0.001** | **<0.001** | 0.67 | 0.81 | 3.7 | T |
| | RT | 4.0 | 10.2 | 5.7 | 6.1 | 4.3 | 3.8 | | | | | | | T |
| Pain | CTRT | 18.4 | 21.6 | 23.5 | 21.1 | 20.5 | 16.2 | 0.008 | 0.04 | 0.09 | **0.0075*** | 0.34 | 25.4 | **S** |
| | RT | 17.1 | 19.1 | 16.9 | 15.6 | 14.1 | 13.5 | | | | | | | **S** |
| **CX 24 subscales/items** | | | | | | | | | | | | | | |
| Symptom experience‡ | CTRT | 9.7 | 16.2 | 12.2 | 11.8 | 12.3 | 12.1 | **<0.001** | 0.6 | 0.0047 | 0.56 | 0.59 | | |
| | RT | 9.5 | 16.9 | 11.8 | 12.5 | 11.7 | 11.5 | | | | | | | |
| Body image‡ | CTRT | 12.0 | 17.2 | 25.3 | 16.9 | 16.4 | 13.7 | **<0.001** | **<0.001** | **<0.001** | **0.0053*** | 0.25 | | |
| | RT | 10.0 | 13.1 | 13.0 | 11.9 | 10.6 | 11 | | | | | | | |
| Sexual functioning‡ | CTRT | 14.3 | 21.3 | 19.0 | 20.4 | 23.4 | 25.3 | 0.059 | 0.53 | **<0.001** | 0.83 | 0.92 | | |
| | RT | 11.5 | 23.2 | 22.5 | 24.3 | 26.0 | 26.2 | | | | | | | |
| **OV 28 subscales** | | | | | | | | | | | | | | |
| Chemotherapy‡ | CTRT | 6.2 | 18.9 | 31.7 | 14.9 | 14.6 | 14.9 | **<0.001** | **<0.001** | **<0.001** | **0.0083** | 0.061 | | |
| | RT | 7.8 | 11.0 | 12.1 | 11.5 | 10.8 | 11.7 | | | | | | | |
| Peripheral neuropathy‡ | CTRT | 5.5 | 14.8 | 47.1 | 32.4 | 28.8 | 23.5 | **<0.001** | **<0.001** | **<0.001** | **<0.001†** | **0.0032*** | | |
| | RT | 5.5 | 8.7 | 12.5 | 11.3 | 13.6 | 16.3 | | | | | | | |

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 Organization for Research and Treatment of Cancer quality of life questionnaire C30; CTRT = combined chemotherapy and radiotherapy; RT = radiotherapy; Norm = age-matched normative population.[16] CX = cervix; OV = ovarian; HRQOL = health-related quality of life; Tx = treatment; *p* Time = changes of quality-of-life scores over time; *p* Tx = difference between the two treatment groups; *p* Time by Tx = difference between the two treatment groups over time; *p* Tx at 3yr = difference between the two treatment groups at 3 years; *p* Tx at 5yr = difference between the two treatment groups at 5 years; CS = clinical significance at 5 years; T = trivial difference; S = small difference; M = medium difference. Bold values denote statistical significance at the $p<0.01$ level; Bold values in the 'Norm'-column denote statistically significant and clinically relevant small/medium differences compared to 5-years study-patients' score.

*Clinically relevant small difference.

†Clinically relevant medium difference.

‡Items included in the subscale are specified in supplementary Table A2.

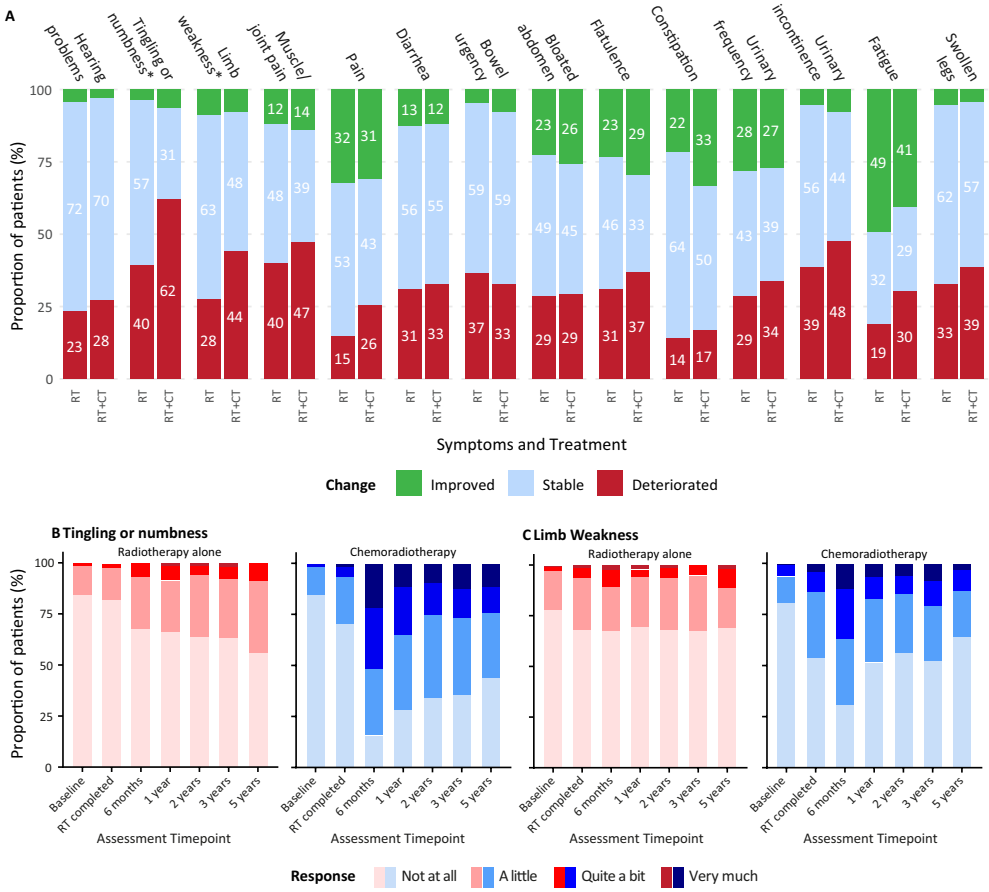


**Figure 3.** Clinically relevant long-term changes compared to baseline in patient reported symptoms on EORTC QLQ-C30, CX24 and OV28 on individual patient level (A) and patient responses on single-items with significant change: tingling or numbness (B) and limb weakness (C).
Long-term change is defined as the mean of 3 and 5 year scores compared to baseline score on individual level. CT = chemotherapy; RT = radiotherapy.

## Symptom items

A complete overview of the proportion of patients reporting significant ("quite a bit" or "very much") symptoms is shown in Appendix Table A2. Patients treated with chemoradiotherapy reported more significant tingling or numbness throughout the 5-year follow-up period compared with patients who received radiotherapy alone. At 5 years, 32 (24%) patients treated with chemoradiotherapy reported significant tingling/numbness, in contrast to 9 (9%) treated with radiotherapy ($p = .002$). Likewise, 129 (62%) versus 66 (40%) patients had deteriorated in tingling/numbness compared with baseline ($p < .001$, Figure 3 and Appendix Figure A5A); no difference between patients with or without diabetes was found among patients treated with chemotherapy (Appendix



Figure A4C and A5B). A trend toward worse tingling/numbness in patients aged ≥70 years was found over time after chemoradiotherapy ($p = .016$) but not after radiotherapy ($p = .35$, Figure A4B). None of variables entered in the multivariate logistic regression model were statistically significant risk factors for tingling/numbness (data not shown).

Chemoradiotherapy patients reported more significant limb weakness up to 3 years (21% after chemoradiotherapy vs 5% after radiotherapy at 3 years, $p < .001$), with deterioration at 3 and 5 years compared with baseline in 92 (44%) patients after chemoradiotherapy versus 46 (28%) after radiotherapy ($p = .003$, Figure 3). No between-group differences in long-term change of gastrointestinal and bladder symptoms were seen (Figure 3).

Sexual activity did not differ between the 2 treatment groups at 3 and 5 years (Appendix Table A2). Sexual activity was reported by 69 (34%) patients (both treatment groups combined) at 5 years. Among those sexually active, 14 (19%) patients reported significant pain during sex; 20 (27%) reported significant vaginal dryness, and 58 (80%) reported sex to be enjoyable. Mean sexual activity scores were lower than those of the age-matched normative population, with a clinically relevant moderate difference ($p < .001$; Appendix Figure A6).

## Correlation

The strongest between-functioning score correlations were found for physical and role functioning ($\tau = 0.66$), for social and role functioning ($\tau = 0.61$), for global health/QOL and role functioning ($\tau = 0.58$), and for global health/QOL and physical functioning ($\tau = 0.53$). The strengths of the negative correlations between symptoms and functioning varied from -0.12 to -0.64, with the strongest correlation for fatigue, closely followed by pain, limb weakness, muscle/joint pain, and lower back pain. The correlation between these symptoms also was relatively strong ($\tau = 0.39$-$0.55$). Finally, there were significant negative correlations for tingling/numbness and physical functioning ($\tau = -0.32$), role functioning ($\tau = -0.30$), global health/QOL ($\tau = -0.26$), and the other functioning scales ($\tau = -0.22$ to $-0.25$). A comprehensive correlation matrix is displayed in Appendix Figure A7.

## Discussion

This long-term analysis of toxicity and HRQOL in the PORTEC-3 trial shows that combined adjuvant chemoradiotherapy for high risk endometrial cancer may have a long-lasting clinically relevant negative impact on quality of life, with a small long-term deterioration in physical and role functioning for the first 3 years after treatment compared with radiotherapy alone. Patients treated with chemoradiotherapy reported significantly more prominent limb weakness until 3 years and persistent tingling or numbness in hands

or feet throughout the 5-year follow-up period. In addition, more grade ≥2 toxicity was reported at 5 years (38% vs 24%). Despite these persistent symptoms, the treatment groups had similar long-term global health/QOL scores that were in fact better than those of the age-matched normative population. This is the first comprehensive documentation of long-term patient-reported symptoms and HRQOL after chemoradiotherapy in endometrial cancer, with the strength of comparison to pelvic radiotherapy alone and to an age-matched normative population, exclusion of biases due to the randomization, and complete follow-up. These data are essential for patient counseling and shared decision making on adjuvant therapy in high risk endometrial cancer.

The present study found remaining grade ≥2 sensory neuropathy in 6% after chemoradiotherapy, with HRQOL showing "quite a bit" or "very much" tingling/numbness being reported by 24% at 5 years. The recovery was largest in the first months after chemotherapy and improved until 2 years to a stable level. In comparison, less than 10% of the patients reported long-term significant tingling/numbness after radiotherapy alone (no reported grade ≥2 AE), which seemed most likely due to diabetic and idiopathic peripheral neuropathy in this elderly population.[20] Because limited agreement between patient and physician scoring of toxicities has been reported,[21] physicians were required to report grade ≥2 AE to focus on more severe toxicities, whereas patient-reported outcomes were used for mild toxicities. Reported data on long-term toxicity and HRQOL of women treated with carboplatin and paclitaxel chemotherapy, although limited, are available from trials of first-line therapy in ovarian cancer. This comparison is relevant because patients with ovarian cancer are of similar age and had previous pelvic surgery without radiotherapy. Similar levels of patient-reported persistent tingling/numbness with a comparable pattern of recovery after chemotherapy were seen in studies of ovarian cancer survivors.[6,9] The randomized GOG-249 trial, in which 3 cycles of carboplatin and paclitaxel with vaginal brachytherapy were compared with pelvic radiotherapy alone in women with high-intermediate and high risk stage I-II endometrial cancer, also showed significantly higher chemotherapy-induced peripheral neuropathy (CIPN) rates in the chemotherapy arm (sensory neuropathy grade ≥2 in 10% at 2 years), even while using only 3 cycles. Detailed analysis on HRQOL in the GOG-249 trial is pending.[22]

Another important persistent symptom after chemoradiotherapy was limb weakness, which might be interpreted as a result of motor CIPN. However, limb weakness was found to be more strongly correlated to fatigue and muscle/joint pain than to tingling/numbness; this finding supports previous studies suggesting that limb weakness is more a general symptom, associated with fatigue and reduced physical functioning.[6,23]





The correlation coefficient ($\tau = 0.32$) found between tingling/numbness and physical functioning means that a patient with a higher tingling/numbness score had a 66% chance of also having a worse functioning score compared with another patient. This suggests that tingling/numbness is associated with impaired functioning, although correlations for other symptoms (limb weakness, fatigue, and pain) and functioning and global health/QOL were stronger. Most nonlongitudinal studies investigating the correlation between sensory neuropathy and functioning in various cancer types found a negative correlation.[6, 7, 8,10,11] Bonhof et al.[9] found significant functioning differences between patients with and without limb weakness, but not for tingling/numbness at 2 years, possibly due to the small sample size. In general, it seems that functioning is negatively influenced by several symptoms, including tingling/numbness, limb weakness, fatigue, and pain.

In this long-term analysis, it seemed that chemoradiotherapy patients further improved between 3 and 5 years of follow-up in physical and role functioning and limb weakness. It is possible that the relatively high attrition rate (around 30%) between 3 and 5 years might introduce some response bias. A small part of the attrition at this timepoint is explained by death or recurrence; however, other reasons for missing questionnaires were not collected. Notably, chemoradiotherapy patients who responded only at 3 years reported significantly more significant muscle/joint pain, symptoms that were strongly correlated to physical and role functioning, than patients who responded both at 3 and 5 years. Another explanation could be that patients adjust their lives to bothersome but manageable symptoms, which is also suggested by the improvement in long-term global health/QOL scores in both treatment groups. Moreover, possible bias due to the Hawthorne effect should be taken into consideration when comparing normative to trial population data; patients participating in trials may report better QOL than normative populations.

One limitation of the study is that toxicity, even though scored by a physician according to the CTCAE classification, remains a subjective measurement. At baseline, grade ≥2 hypertension was scored in 27% of the patients, corresponding to the on-study form reporting 33% patients having hypertension with medication. At subsequent timepoints, hypertension was only scored in about 10% of the patients. This implies that during and after therapy, oncologists focus on treatment-related AE, resulting in underreporting of unrelated conditions primarily managed by family doctors such as hypertension, which is especially important in interpreting changes from baseline. Because the bias occurred in both groups, it has negligible impact on long-term between-group comparison.

The contemporary challenge is to avoid significant symptoms caused by chemotherapy by developing preventive strategies and intervention measures. Unfortunately, there is currently no effective treatment or prevention strategy against CIPN.[24] This study was unable to identify risk factors for persistent CIPN, which is unfortunate because data on risk factors for developing CIPN are inconsistent.[25] Limitations to drawing any conclusion include the selected study population based on inclusion criteria and insufficient power related to small groups. Nevertheless, patients aged 70 years or older scored generally worse over time than younger patients, even though this was a selected population of relatively fit women. This age-based difference, particularly for global health/QOL and symptoms of pain, fatigue and tingling/numbness is more pronounced after chemoradiotherapy compared with radiotherapy. Older patients seemed to have a relatively greater failure-free survival benefit from chemotherapy.[12] Therefore, specific patient counseling is recommended for older patients.

No between-group differences were found for gastrointestinal and bladder symptoms, largely explained by the use of pelvic radiotherapy in both arms. The reported gastrointestinal symptoms (eg, urgency and diarrhea in about 10% of the patients) and bladder symptoms (urgency ±25%, incontinence ±10%) are consistent with the rates found after pelvic radiotherapy in the PORTEC-2 trial.[26] The incidence of gastrointestinal symptoms is expected to remain more or less stable, and urinary symptoms are expected to slightly deteriorate in the following years owing to the combined effects of radiotherapy and aging on the pelvic floor and bladder.[3,4]

The overall survival benefit of chemoradiotherapy compared with radiotherapy alone in high risk endometrial cancer was 5% at 5 years for the complete trial population, with the greatest benefit of ≥10% observed in women with serous cancers and those with stage III disease.[2] Molecular classification can be used to more effectively identify subgroups that benefit most from chemotherapy.[27] For example, molecular classification in clinical diagnostics might lead to the specific recommendation of chemoradiotherapy in those with *TP53*-mutated tumors, and chemotherapy might be omitted in *POLE*mut and mismatch repair deficient tumors. Women with high risk mismatch repair deficient tumors might be better treated with adjuvant immunotherapy, with a different but generally more favorable toxicity profile than carboplatin-paclitaxel chemotherapy.

The trade-off between the benefit and the short- and long-term toxicities of chemotherapy should be discussed as part of shared decision making. To better guide shared decision making, it is important to know what patients consider important in this trade-off. In a patient preference study done by the ANZGOG group among their PORTEC-3 participants, more than 50% of women reported a 5% survival improvement as being sufficient to make chemotherapy worthwhile.[28] No study to date has examined which factors are prioritized by patients and clinicians in this decision-making process and what survival improvement would be sufficient to make chemotherapy worthwhile based on the actual symptoms and HRQOL impairment in the PORTEC-3 trial. This is currently being investigated in a Dutch trade-off study in patients with high risk endometrial cancer and their health care professionals.





## Conclusions

This study shows a long-lasting, clinically relevant, negative impact of combined chemotherapy and radiotherapy on toxicity and qulaity of life compared with radiotherapy alone, with persistent peripheral sensory neuropathy at 5 years in 24% of patients and small but clinically relevant differences in physical and role functioning until 3 years. These results provide essential information to be used for patient counseling and shared decision making.

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# APPENDIX A

**Table A1.** Questionnaire response during follow up

| | **Questionnaire time points** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Months | | | | | |
| | Baseline | After RT | 6 | 12 | 18 | 24 | 36 | 60 |
| Responders CT+RT (*n*) | 292 | 236 | 223 | 238 | 217 | 214 | 194 | 132 |
| Responders RT (*n*) | 282 | 231 | 214 | 201 | 189 | 185 | 159 | 103 |
| Responders Total (*n*) | 574 | 467 | 437 | 439 | 406 | 399 | 353 | 235 |
| Patients on assessment (*n*) | 660 | 552 | 528 | 487 | 458 | 417 | 395 | 374 |
| Available data rate[a] | 87% | 71% | 66% | 67% | 62% | 61% | 53% | 36% |
| Completion rate[b] | 87% | 85% | 83% | 90% | 89% | 96% | 89% | 63% |

CT = chemotherapy, RT = radiotherapy.

[a] Calculation of the 'fixed' denominator rate: Numerator as 'number of patients on PRO assessment submitting the PRO assessment at the designated time point' and denominator as 'number of patients in the PRO study population (all study patients, *n* = 660)'.

[b] Calculation of the 'variable' denominator rate: Numerator as 'number of patients on PRO assessment submitting the PRO assessment at the designated time point' and denominator as 'Number of patients on PRO assessment at the designated time point (Patients on assessment = total study population with completed baseline questionnaire excluding deceased patients or patients with recurrent disease)'. Used terms are defined according to SISAQOL recommendations.[1]

**Table A2.** Complete overview of percentages of patients reporting 'quite a bit' or 'very much' HRQOL symptoms using the EORTC QLQ-C30 and subscales of CX-24 and OV-28.

| | | Questionnaire time points | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | After RT | 6m | 12m | 24m | 36m | 60m | *p*-value Time | Tx | Time by Tx | Tx at 3 years | Tx at 5 years |
| **QLQ-C30 symptoms** | | | | | | | | | | | | | |
| Dyspnoea | CTRT | 5.4 | 11.0 | 15.4 | 7.5 | 8.0 | 11.2 | 8.5 | 0.0040 | 0.030 | 0.16 | 0.14 | 0.83 |
| | RT | 2.8 | 5.2 | 5.1 | 5.0 | 4.1 | 6.3 | 5.8 | | | | | |
| Insomnia | CTRT | 24.5 | 25.2 | 25.1 | 17.8 | 18.8 | 23.5 | 19.8 | 0.34 | 0.50 | 0.75 | 0.11 | 0.10 |
| | RT | 18.8 | 19.0 | 18.6 | 14.6 | 12.4 | 14.4 | 10.7 | | | | | |
| Appetite loss | CTRT | 6.4 | 23.6 | 11.2 | 2.5 | 3.3 | 3.6 | 5.3 | <0.001 | 0.038 | 0.15 | 0.8 | 0.10 |
| | RT | 4.5 | 15.7 | 4.7 | 3.4 | 3.6 | 3.8 | 1.0 | | | | | |
| Constipation | CTRT | 11.5 | 4.6 | 8.2 | 3.7 | 4.7 | 7.3 | 5.3 | 0.0047 | 0.059 | 0.12 | 0.14 | 0.42 |
| | RT | 7.0 | 1.3 | 1.9 | 4.0 | 3.1 | 2.5 | 2.9 | | | | | |
| Diarrhoea | CTRT | 5.1 | 36.1 | 12.7 | 10.4 | 9.9 | 11.8 | 14.5 | <0.001 | 0.96 | 0.024 | 0.63 | 0.23 |
| | RT | 3.8 | 36.8 | 12.6 | 11.3 | 10.9 | 10.1 | 7.8 | | | | | |
| Financial difficulties | CTRT | 12.2 | 11.9 | 15.9 | 8.7 | 6.5 | 6.6 | 2.3 | <0.001 | 0.012 | 0.0083 | 0.16 | 0.044 |
| | RT | 7.7 | 7.5 | 7.0 | 3.0 | 4.2 | 3.1 | 4.9 | | | | | |
| **CX24** | | | | | | | | | | | | | |
| **Bowel symptoms** | | | | | | | | | | | | | |
| 1. Abdominal cramps | CTRT | 6.8 | 17.8 | 9.9 | 9.2 | 10.8 | 9.7 | 6.1 | <0.001 | 0.79 | 0.86 | 0.2 | 0.66 |
| | RT | 6.0 | 15.5 | 9.0 | 10.4 | 7.3 | 6.3 | 7.8 | | | | | |
| 1. Difficulty controlling bowels | CTRT | 3.1 | 20.3 | 9.9 | 9.1 | 7.5 | 9.7 | 9.2 | <0.001 | 0.61 | 0.0012 | 0.43 | 0.87 |
| | RT | 1.4 | 20.3 | 10.9 | 10.4 | 12.2 | 8.2 | 8.7 | | | | | |
| 1. Blood in stools | CTRT | 0.7 | 0.8 | 0.9 | 0.0 | 2.4 | 0.0 | 0.8 | 0.70 | 0.96 | 1.00 | 0.90 | 0.92 |
| | RT | 0.4 | 0.4 | 0.9 | 0.5 | 0.5 | 0.6 | 0.0 | | | | | |
| **Urinary symptoms** | | | | | | | | | | | | | |
| 1. Urninary frequency | CTRT | 23.3 | 38.6 | 22.1 | 23.0 | 17.5 | 23.5 | 27.3 | <0.001 | 0.89 | 0.83 | 0.93 | 0.85 |
| | RT | 21.8 | 36.6 | 16.9 | 22.8 | 20.4 | 20.9 | 22.5 | | | | | |
| 1. Dysuria | CTRT | 5.8 | 17.3 | 1.4 | 2.5 | 1.9 | 3.1 | 2.3 | <0.001 | 0.67 | 0.31 | 0.51 | 0.76 |
| | RT | 4.2 | 14.7 | 3.8 | 3.0 | 1.6 | 1.3 | 1.0 | | | | | |
| 1. Urinary leakage | CTRT | 2.7 | 6.8 | 8.6 | 7.9 | 9.3 | 16.4 | 10.6 | <0.001 | 0.034 | <0.001 | 0.026 | 0.94 |
| | RT | 4.2 | 4.3 | 4.7 | 8.9 | 9.9 | 8.9 | 10.7 | | | | | |
| 1. Difficulty emptying the bladder | CTRT | 4.4 | 5.1 | 2.3 | 1.7 | 2.8 | 5.7 | 3.8 | 0.12 | 0.39 | 0.40 | 0.12 | 0.77 |
| | RT | 3.2 | 4.8 | 2.8 | 3.5 | 3.7 | 1.9 | 3.9 | | | | | |
| **Other** | | | | | | | | | | | | | |
| Swollen legs | CTRT | 2.4 | 5.5 | 18.0 | 16.3 | 12.7 | 7.6 | 15.3 | <0.001 | 0.10 | <0.001 | 0.018 | 0.47 |
| | RT | 2.5 | 3.0 | 11.3 | 10.9 | 14.1 | 16.9 | 13.6 | | | | | |
| 1. Lower back pain | CTRT | 10.5 | 10.2 | 16.6 | 18.8 | 18.7 | 22.2 | 22.3 | <0.001 | 0.86 | 0.0079 | 0.40 | 0.13 |
| | RT | 9.2 | 7.8 | 16.0 | 14.3 | 16.6 | 14.6 | 12.7 | | | | | |

**Table A2.** Complete overview of percentages of patients reporting 'quite a bit' or 'very much' HRQOL symptoms using the EORTC QLQ-C30 and subscales of CX-24 and OV-28 *(continued)*.

| | | Questionnaire time points | | | | *p*-value | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | After RT | 6m | 12m | 24m | 36m | 60m | Time | Tx | Time by Tx | Tx at 3 years | Tx at 5 years |
| Tingling/numbness | CTRT | 1.7 | 6.4 | 51.8 | 34.9 | 25.2 | 26.8 | 24.2 | <0.001 | <0.001 | <0.001 | <0.001 | 0.0026 |
| | RT | 1.4 | 2.6 | 6.7 | 8.5 | 5.8 | 7.6 | 8.8 | | | | | |
| 1. Irritation/soreness vagina/vulva | CTRT | 2.7 | 8.1 | 5.0 | 3.8 | 1.4 | 2.1 | 4.6 | 0.001 | 0.33 | 0.14 | 0.18 | 0.62 |
| | RT | 1.4 | 11.7 | 3.8 | 5.5 | 3.1 | 3.8 | 4.9 | | | | | |
| 1. Vaginal discharge | CTRT | 2.7 | 2.6 | 2.3 | 2.1 | 0.9 | 2.5 | 1.5 | 0.98 | 0.91 | 0.89 | 0.57 | 0.81 |
| | RT | 1.8 | 4.3 | 0.5 | 1.5 | 0.5 | 1.5 | 1.9 | | | | | |
| 1. Vaginal bleeding abnormal | CTRT | 0.7 | 1.3 | 1.3 | 1.3 | 0.5 | 0.0 | 0.8 | 0.95 | 0.98 | 0.99 | 0.88 | 0.86 |
| | RT | 1.0 | 0.4 | 0.9 | 0.5 | 0.5 | 0.6 | 0.0 | | | | | |
| Hot flushes and/or sweats | CTRT | 16.9 | 14.8 | 20.4 | 18.8 | 17.2 | 20.9 | 14.4 | 0.19 | 0.37 | 0.27 | 0.94 | 0.97 |
| | RT | 12.7 | 15.6 | 24.5 | 22.8 | 22.0 | 22.0 | 15.5 | | | | | |
| **Body Image** | | | | | | | | | | | | | |
| 2. Feeling of physically less attractive | CTRT | 5.5 | 14.4 | 26.1 | 11.1 | 8.9 | 10.8 | 8.3 | <0.001 | <0.001 | 0.34 | 0.046 | 0.17 |
| | RT | 3.4 | 6.9 | 7.5 | 4.4 | 4.2 | 5.1 | 3.9 | | | | | |
| 2. Feeling less feminine | CTRT | 5.1 | 9.3 | 16.1 | 10.8 | 8.4 | 10.3 | 5.3 | <0.001 | 0.044 | 0.71 | 0.014 | 0.38 |
| | RT | 3.5 | 7.0 | 6.6 | 5.4 | 4.7 | 4.5 | 3.9 | | | | | |
| 2. Dissatisfied with body | CTRT | 5.8 | 10.5 | 18.1 | 13.6 | 11.6 | 14.9 | 15.2 | <0.001 | 0.37 | 0.0041 | 0.39 | 0.09 |
| | RT | 3.9 | 8.8 | 9.4 | 9.4 | 6.3 | 10.1 | 6.9 | | | | | |
| **Sexual functioning** | | | | | | | | | | | | | |
| Worries about sex | CTRT | 13.8 | 21.5 | 20.1 | 17.1 | 12.8 | 14.6 | 11.1 | 0.049 | 0.57 | 0.64 | 0.15 | 0.41 |
| | RT | 14.3 | 20.2 | 15.3 | 13.6 | 14.0 | 9.5 | 17.2 | | | | | |
| Sexual activity† | CTRT | 11.9 | 18.6 | 29.2 | 33.9 | 33.5 | 33.5 | 30.8 | <0.001 | 0.14 | <0.001 | 0.48 | 0.10 |
| | RT | 9.7 | 21.5 | 41.9 | 42.2 | 36.0 | 37.3 | 37.0 | | | | | |
| 3. Vaginal dryness* | CTRT | 10.0 | 18.8 | 24.6 | 29.9 | 22.4 | 28.1 | 21.6 | 0.22 | 0.63 | 0.029 | 0.5 | 0.43 |
| | RT | 4.3 | 23.6 | 21.1 | 24.2 | 31.3 | 28.8 | 31.6 | | | | | |
| 3. Shortness of vagina* | CTRT | 4.2 | 8.5 | 10.1 | 15.8 | 21.5 | 22.4 | 13.2 | 0.24 | 0.96 | 0.10 | 0.62 | 0.98 |
| | RT | 2.2 | 10.9 | 14.1 | 18.9 | 22.7 | 15.5 | 21.6 | | | | | |
| 3. Tightness of vagina* | CTRT | 6.4 | 27.6 | 19.4 | 17.1 | 15.2 | 29.3 | 13.5 | 0.038 | 0.071 | 0.0037 | 0.42 | 0.46 |
| | RT | 4.3 | 13.0 | 21.3 | 21.1 | 25.0 | 20.7 | 24.3 | | | | | |
| 3. Pain during sexual intercourse* | CTRT | 0.0 | 25.0 | 16.2 | 10.7 | 11.9 | 19.6 | 8.1 | 0.15 | 0.22 | 0.023 | 0.92 | 0.13 |
| | RT | 4.7 | 18.3 | 17.0 | 20.9 | 23.5 | 20.0 | 29.7 | | | | | |
| Sexual activity enjoyable?*† | CTRT | 50.0 | 57.5 | 75.0 | 77.8 | 81.8 | 80.4 | 83.8 | 0.056 | 0.49 | 0.30 | 0.46 | 0.77 |
| | RT | 61.0 | 74.5 | 75.0 | 77.8 | 76.1 | 83.1 | 75.0 | | | | | |
| **OV28** | | | | | | | | | | | | | |
| Bloated feeling abdomen/stomach | CTRT | 13.0 | 1.7 | 19.5 | 11.3 | 11.3 | 11.9 | 13.0 | 0.054 | 0.59 | 0.56 | 0.69 | 0.42 |
| | RT | 11.2 | 14.4 | 14.4 | 15.3 | 10.5 | 12.1 | 10.0 | | | | | |

**Table A2.** Complete overview of percentages of patients reporting 'quite a bit' or 'very much' HRQOL symptoms using the EORTC QLQ-C30 and subscales of CX-24 and OV-28 *(continued)*.

| | | Questionnaire time points | | | | *p*-value | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | After RT | 6m | 12m | 24m | 36m | 60m | Time | Tx | Time by Tx | Tx at 3 years | Tx at 5 years |
| Passing wind/gas/flatulence | CTRT | 17.6 | 20.3 | 24.0 | 21.3 | 22.4 | 21.4 | 22.3 | 0.7 | 0.52 | 0.43 | 0.29 | 0.25 |
| | RT | 11.8 | 18.7 | 19.6 | 21.3 | 17.6 | 15.9 | 14.9 | | | | | |
| 4. Loss of any hair | CTRT | 1.4 | 11.1 | 45.2 | 4.6 | 0.5 | 2.1 | 3.9 | <0.001 | <0.001 | <0.001 | 0.24 | 0.41 |
| | RT | 0.4 | 3.1 | 4.3 | 3.0 | 2.1 | 0.6 | 2.0 | | | | | |
| 4. Upset by loss of hair** | CTRT | 3.3 | 25.0 | 41.9 | 29.3 | 11.1 | 16.2 | 20.0 | <0.001 | 0.013 | 0.26 | 0.28 | 0.11 |
| | RT | 5.3 | 3.6 | 15.9 | 9.3 | 7.3 | 6.1 | 4.8 | | | | | |
| 4. Different taste of food and drink | CTRT | 3.5 | 26.2 | 22.3 | 3.9 | 1.9 | 4.2 | 4.0 | <0.001 | <0.001 | 0.46 | 0.11 | 0.86 |
| | RT | 0.7 | 9.4 | 4.3 | 1.5 | 1.6 | 1.9 | 0.0 | | | | | |
| 5. Tingling hand/feet | CTRT | 1.1 | 7.2 | 49.3 | 26.8 | 23.4 | 25.4 | 21.4 | <0.001 | <0.001 | <0.001 | <0.001 | 0.018 |
| | RT | 1.4 | 2.2 | 5.8 | 4.1 | 5.4 | 4.5 | 10.2 | | | | | |
| 5. Numbness fingers/toes | CTRT | 1.4 | 5.5 | 50.0 | 29.6 | 25.5 | 24.4 | 19.7 | <0.001 | <0.001 | <0.001 | <0.001 | 0.029 |
| | RT | 0.4 | 2.7 | 4.9 | 2.6 | 4.3 | 8.3 | 8.3 | | | | | |
| 5. Weakness arms/legs | CTRT | 6.3 | 14.2 | 36.8 | 17.5 | 15.1 | 20.7 | 13.3 | <0.001 | <0.001 | <0.001 | <0.001 | 0.52 |
| | RT | 2.9 | 6.3 | 11.0 | 5.7 | 6.3 | 5.1 | 11.3 | | | | | |
| 4. Muscle or joint pain | CTRT | 9.5 | 16.9 | 37.8 | 25.1 | 24.5 | 28.4 | 23.3 | <0.001 | 0.045 | <0.001 | 0.033 | 0.19 |
| | RT | 7.0 | 12.6 | 21.7 | 17.3 | 17.2 | 16.3 | 16.8 | | | | | |
| 4. Problems hearing | CTRT | 2.5 | 3.0 | 11.4 | 6.8 | 7.6 | 10.3 | 11.5 | <0.001 | 0.24 | 0.0014 | 0.049 | 0.057 |
| | RT | 2.2 | 1.3 | 4.8 | 5.1 | 3.7 | 5.8 | 4.1 | | | | | |

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire C30; CTRT = combined chemotherapy and radiotherapy; RT = radiotherapy; CX = cervix; OV = ovarian; HRQOL = health-related quality of life; Tx = treatment; *p* time = changes of quality-of-life scores over time; *p* Tx = difference between the two treatment groups; *p* time by Tx = difference between the two treatment groups over time; *p* Tx at 3 years = difference between the two treatment groups at 3 years; *p* Tx at 5 years = difference between the two treatment groups at 5 years.

* 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.

† Percentages of patients reporting 'a little', 'quite a bit' or 'very much'.

1. Symptom experience subscale; 2. Body image subscale; 3. Sexual functioning subscale; 4. Chemotherapy subscale; 5. Peripheral neuropathy subscale.

**Table A3.** Characteristics of responders versus non-responders at baseline.

| | Non-Responders *n* = 86 | Responders *n* = 574 | *p*-value |
|---|---|---|---|
| **Age at randomization (y)** | | | 0.659 |
| <60 | 36 (41.9) | 232 (40.4) | |
| 60-69 | 32 (37.2) | 240 (41.8) | |
| ≥70 | 18 (20.9) | 102 (17.8) | |
| **WHO performance score** | | | **0.001** |
| 0-1 | 80 (94.1) | 567 (99.1) | |
| 2 | 5 (5.9) | 5 (0.9) | |
| **Comorbidities** | | | |
| Diabetes | 12 (14.0) | 69 (12.1) | 0.748 |
| Hypertension | 26 (30.6) | 194 (33.8) | 0.644 |
| Cardiovascular | 9 (10.5) | 40 (7.0) | 0.363 |
| **Country** | | | **<0.001** |
| The Netherlands | 36 (41.9) | 102 (17.8) | |
| United Kingdom | 20 (23.3) | 157 (27.4) | |
| Australia & New Zealand | 2 ( 2.3) | 116 (20.2) | |
| France | 11 (12.8) | 53 (9.2) | |
| Italy | 13 (15.1) | 85 (14.8) | |
| Canada | 4 ( 4.7) | 61 (10.6) | |
| **FIGO 2009 stage** | | | 0.136 |
| Ia | 12 (14.0) | 66 (11.5) | |
| Ib | 21 (24.4) | 96 (16.7) | |
| II | 15 (17.4) | 155 (27.0) | |
| III | 38 (44.2) | 257 (44.8) | |
| **Type of surgery** | | | 0.681 |
| TAH-BSO | 28 (32.6) | 163 (28.4) | |
| TAH-BSO with LND or full staging | 36 (41.8) | 240 (41.8) | |
| TLH-BSO | 12 (14.0) | 76 (13.2) | |
| TLH-BSO with LND or full staging | 10 ( 11.7) | 95 (16.6) | |
| **Radiotherapy** | | | |
| RT completion | 85 ( 98.8) | 569 (99.1) | 1.000 |
| Brachytherapy boost | 34 ( 39.5) | 275 (48.0) | 0.177 |

Data are *n* (%). FIGO = International Federation of Gynaecology and Obstetrics. EEC = endometrioid endometrial carcinoma. TAH = total abdominal hysterectomy. BSO = bilateral salpingo-oopherectomy. TLH = total laparoscopic hysterectomy. RT = radiotherapy.





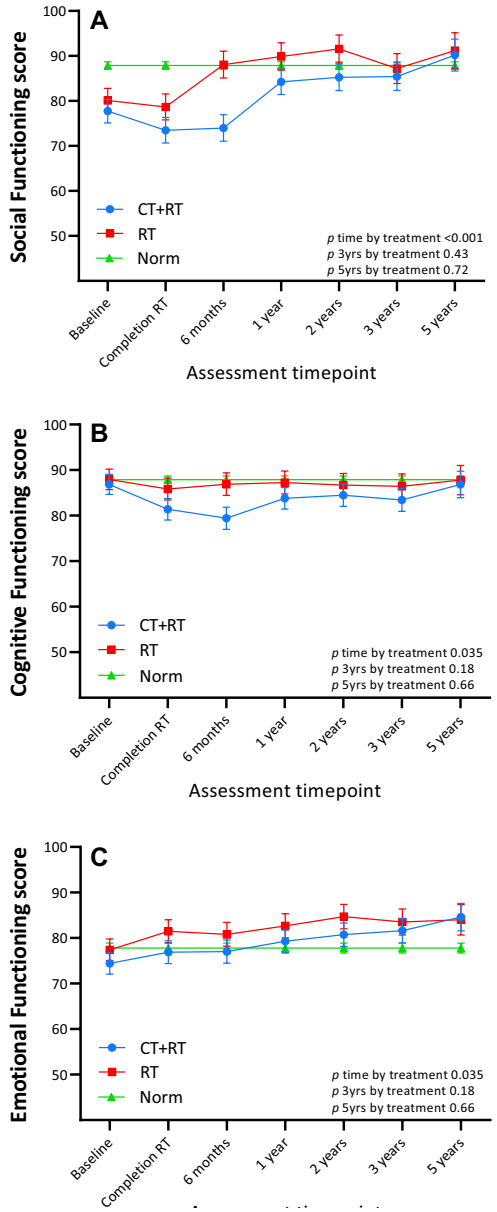



**Figure A1.** Patient functioning on subscales from EORTC QLQ-C30 for Social functioning (A), Cognitive functioning (B), Emotional functioning (C).

A higher score indicates a higher level of functioning or activity. Error bars show 95% CI. EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; *p* time by treatment = difference between the two treatment groups over time; *p* 3yrs by treatment = difference between the two treatment groups at 3 years; *p* 5yrs by treatment = difference between the two treatment groups at 5 years; CT = chemotherapy; Norm = mean scores of age-match normative data based on women aged 60-69 years across 13 European countries, Canada and the United States;[2] RT = radiotherapy.

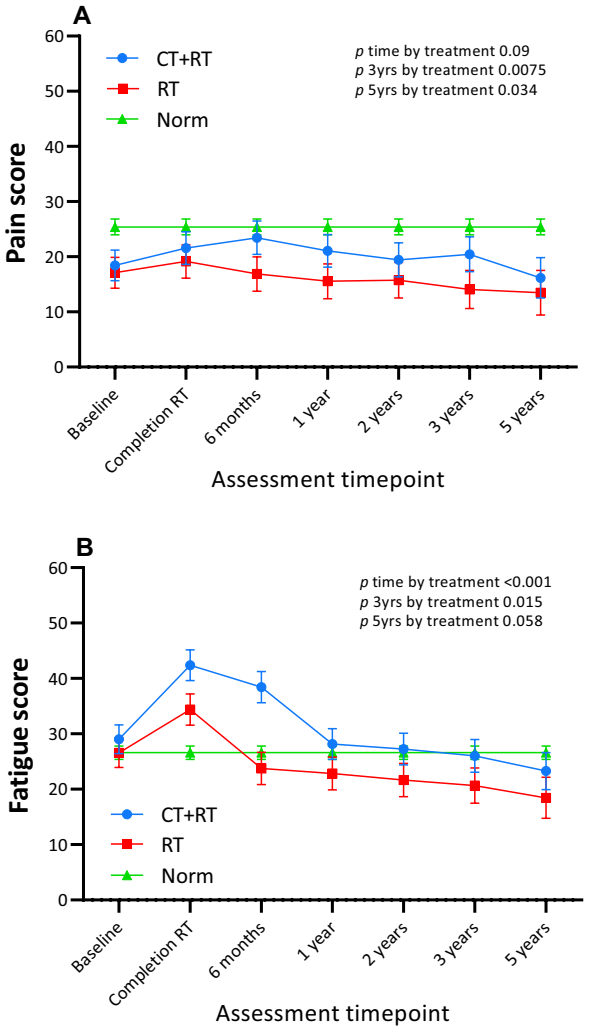



**Figure A2.** Symptoms scales form EORTC QLQ-C30 for pain (A) and fatigue (B).
A higher score indicates a higher level of symptoms. Error bars show 95% CI. EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; *p* time by treatment = difference between the two treatment groups over time; *p* 3yrs by treatment = difference between the two treatment groups at 3 years; *p* 5yrs by treatment = difference between the two treatment groups at 5 years; CT = chemotherapy; Norm = mean scores of age-match normative data based on women aged 60-69 years across 13 European countries, Canada and the United States;[2] RT = radiotherapy.





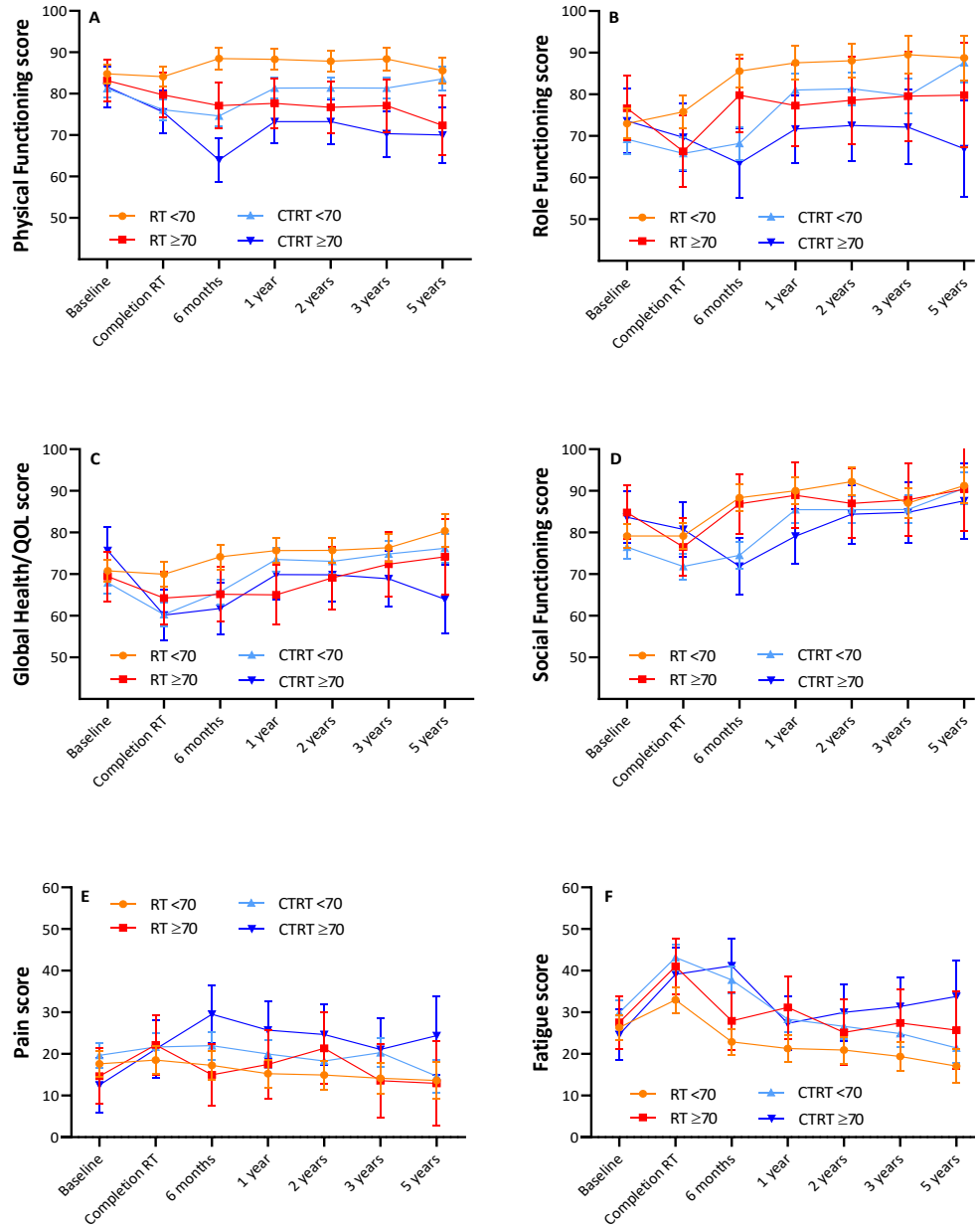



**Figure A3.** Patient functioning and symptom scales from EORTC QLQ-C30 for physical functioning (A), role functioning (B), global health status/quality of life (C), social functioning (D), pain (E) and fatigue(F). Mean estimates calculated by linear mixed models. For functioning scores (A-D), a higher score indicates a higher level of functioning or activity. For symptom scores (A-B), a higher score indicates a higher level of symptoms. Error bars show 95% CI. EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; <70 = patients aged under 70 years; ≥70 = patients aged 70 years and older; CT = chemotherapy; RT = radiotherapy.

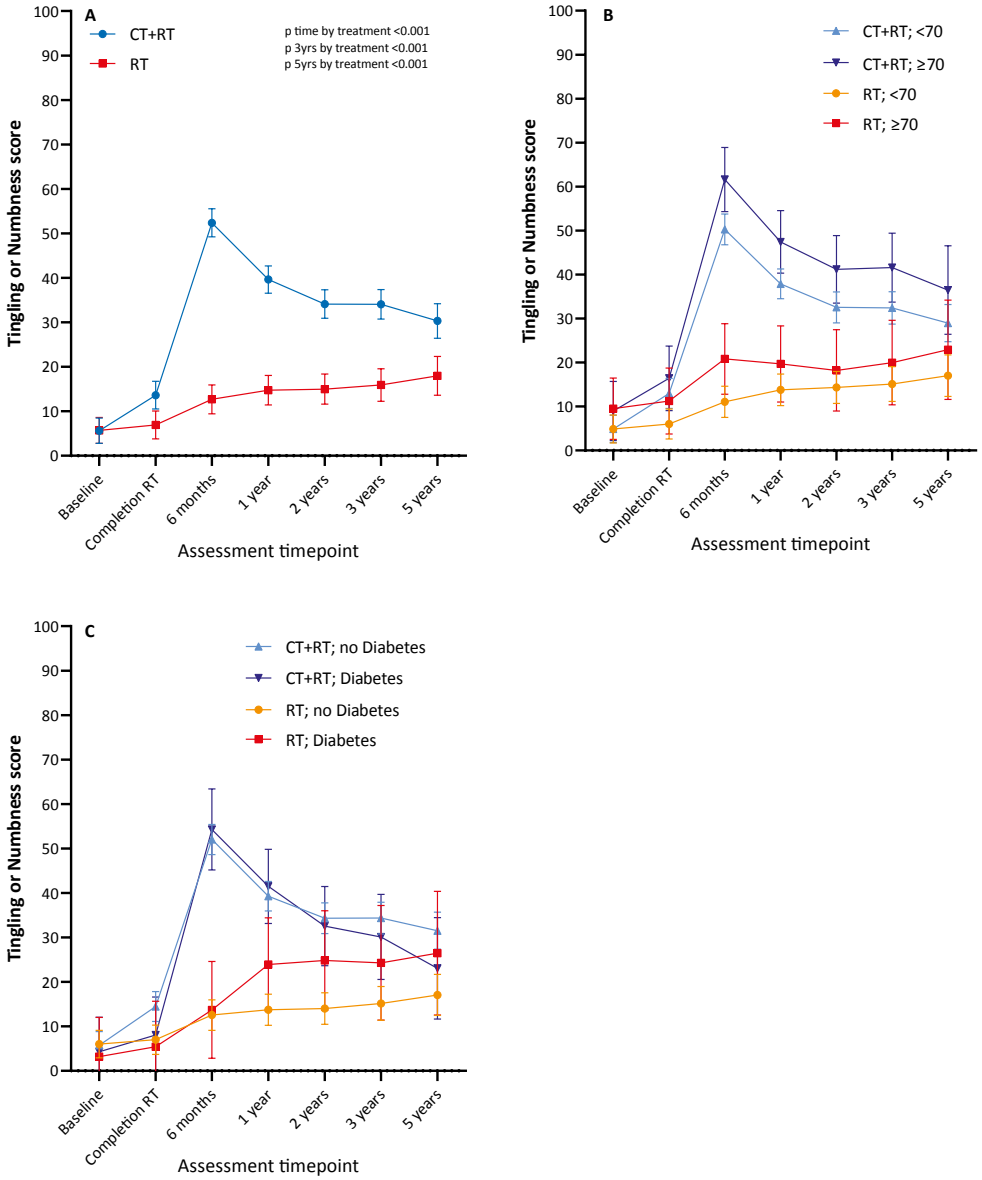
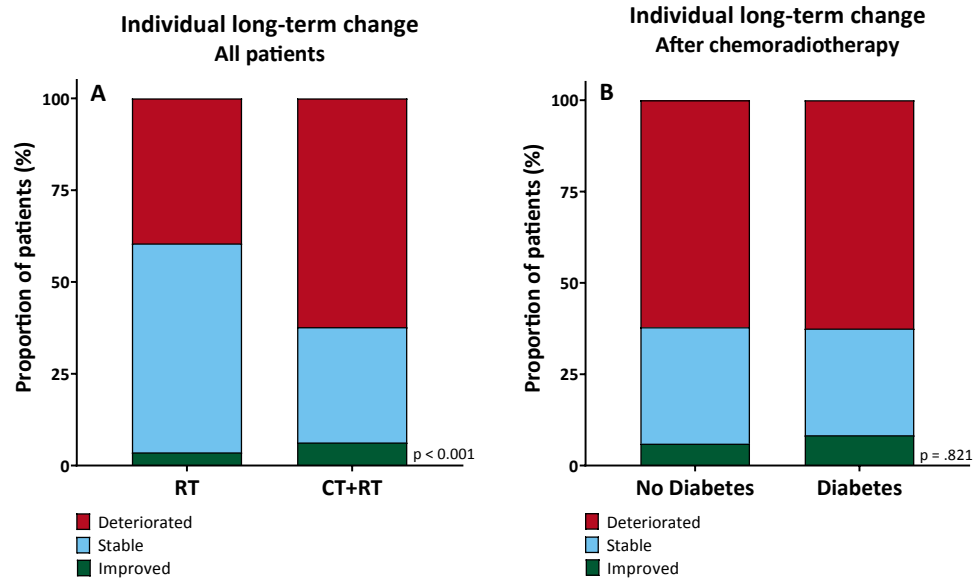



**Figure A4.** Tingling or numbness item score from EORTC QLQ-CX24 for all patients by received treatment (A) combined with age (B) and diabetes (C).
A higher score indicates a higher level of symptoms. Error bars show 95% CI. EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; <70 = patient age under 70 years; ≥70 = patient age 70 years and older; CT = chemotherapy; RT = radiotherapy.





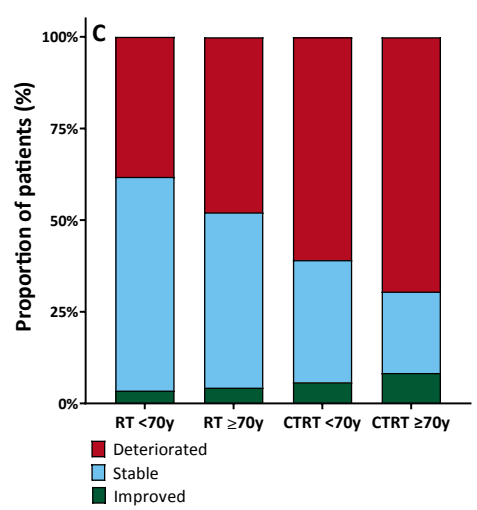




**Figure A5.** Individual definitive improvement, deterioration or stable state from baseline to long-term (3/5 years) EORTC QLQ-CX24 tingling or numbness item assessment of all patients by received treatment (A), the patients who received chemoradiotherapy by diabetes (B) and all patients by received treatment and age (C).

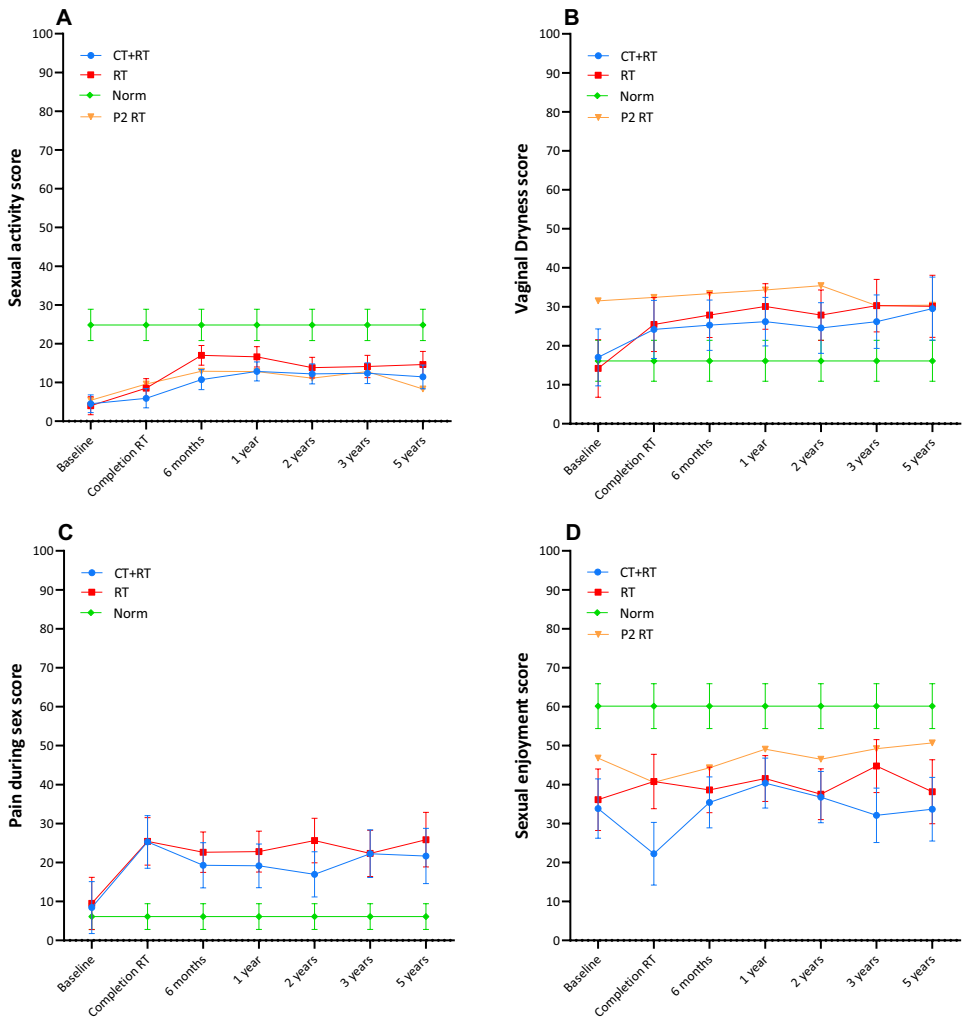



**Figure A6.** Sexual activity and symptoms scales form EORTC QLQ-CX24 for Sexual activity (A), Vaginal dryness (B), Pain during Sex (C) and Sexual enjoyment (D).

A higher score indicates a higher level of sexual activity and a higher level of symptoms. Error bars show 95% CI. EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervix 24 module; CT = chemotherapy; Norm = mean scores of age-match normative data based on Dutch women aged 60-69 years;[3] RT = radiotherapy; P2 RT = pelvic radiotherapy arm of PORTEC-2 trial.[4]





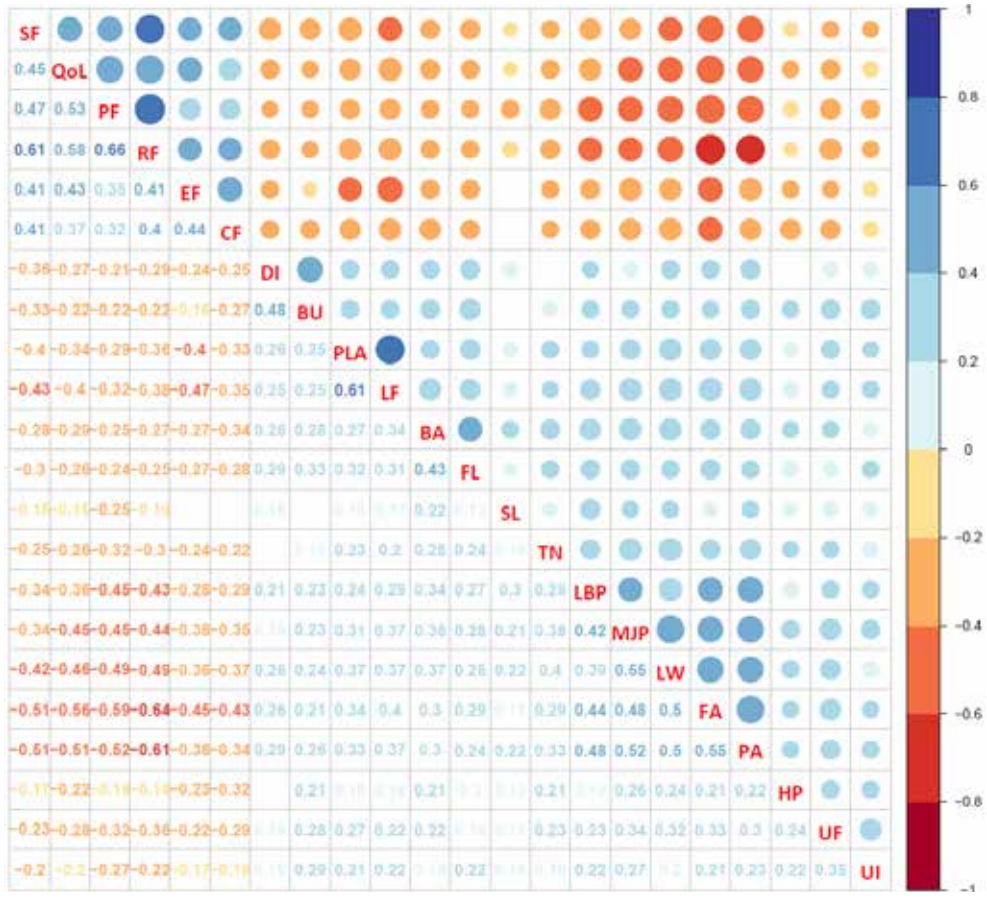



**Figure A7.** Kendall's rank correlation coefficient matrix of functioning scores and symptom items from EORTC QLQ-C30, CX24 and OV28 at 3/5 years.

Blank regions indicate correlation coefficient (τ) is not significant. Displayed coefficients (τ) are significant at the 0.01 level. SF = Social Functioning; QoL = Global Health/Quality of Life; PF = Physical Functioning; RF = Role Functioning; EF = Emotional Functioning; CF = Cognitive Functioning; DI = Diarrhea; BU = Bowel Urgency; PLA = Feeling Physically Less Attractive; LF = Feeling Less Feminine; BA = Bloated Abdomen; FL = Flatulence; SL = Swollen Legs; TN = Tingling or Numbness; LBP = Lower Back Pain; MJP = Muscle or Joint Pain; LW = Limb Weakness; FA = Fatigue; PA = Pain; HP = Hearing Problems; UF = Urinary Frequency; UI = Urinary Incontinence. Interpretation of τ: The calculations are based on concordant and discordant pairs. For example, suppose patient 1 has a better emotional functioning (ef) than patient 2. If patient 1 also has a better cognitive functioning (cf) than patient 2, the patients have the same relative rank orders and they are concordant pairs with respect to ef and cf. However, if patient 2 has a better cf score, then the patients are discordant pairs. If the number of concordant pairs is much larger than the number of discordant pairs, then the random variables are positively correlated. If the number of concordant pairs is much less than discordant pairs, then the variables are negatively correlated. Finally, if the number of concordant pairs is about the same as discordant pairs, then the variables are weakly correlated. τ = 0.60 means 80% of the pairs are concordant, τ = 0.40 means 70% of the pairs are concordant, τ = 0.20 means 60% of the pairs are concordant (τ = 2 * '% concordant pairs' - 1).

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