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Clinical Investigation

Long-Term Toxicity and Health-Related Quality of Life After Adjuvant Chemoradiation Therapy or Radiation Therapy Alone for High-Risk Endometrial Cancer in the Randomized PORTEC-3 Trial

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Purpose: The survival results of the PORTEC-3 trial showed a significant improvement in both overall and failure-free survival with chemoradiation therapy versus pelvic radiation therapy 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 chemoradiation therapy (2 concurrent cycles of cisplatin followed by 4 cycles of carboplatin/paclitaxel) or radiation therapy 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 $\geq$2 AE were scored for 78 (38%) patients who had received chemoradiation therapy versus 46 (24%) who had received radiation therapy alone ($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 $\geq$2 persisted after chemoradiation therapy in 6% (vs 0% after radiation therapy, $P < .001$) 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 chemoradiation therapy 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 chemoradiation therapy 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 nonendometrioid 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 radiation therapy 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 radiation therapy and chemotherapy versus pelvic radiation therapy 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 0.70, $P = .034$) and 7% (76% vs 69%, hazard ratio 0.70, $P = .016$) after chemoradiation therapy. 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 radiation therapy 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 chemoradiation therapy. 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 chemoradiation therapy.[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 radiation therapy (48.6 Gy in 1.8 Gy fractions, with a brachytherapy boost in case of cervical stromal involvement) or chemoradiation therapy (2 cycles of cisplatin 50 mg/m^2 in weeks 1 and 4 of radiation therapy, followed by 4 cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2 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 $\geq$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 radiation therapy, 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 χ^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 $\geq$10-point increase or decrease, and a stable score was defined as a $<$10-point change. Changes were compared between treatment groups using the Fisher exact test. In addition, Kendall's rank correlation was used post hoc to measure the ordinal association between different HRQOL items and scales. Finally, stepwise binary logistic regression with likelihood ratio test–based backward selection was performed to identify risk factors for developing tingling/numbness, including diabetes, cardiovascular disease, hypertension, age ($\geq$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 $\leq.01$ 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 radiation therapy alone and 327 patients received chemoradiation therapy. 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 chemoradiation therapy group and 282 in the radiation therapy-alone group). At 3 years, the completion rate was 89%, and at 5 years it was 63% (Table E1). 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 $\geq$2 in 5 (1%) of the 574 responders versus 5 (6%) of the 86 nonresponders ($P = .005$, Table E3). 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.

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 $\geq$2 baseline AE were scored for 143 (44%) patients in the chemoradiation therapy group and 124 (37%) patients in the radiation therapy group. The most frequently scored AE was hypertension (27%). At 5 years, grade $\geq$2 AE were reported for 78 (38%) patients who had received chemoradiation therapy versus 46 (24%) patients who had received radiation therapy ($P = .008$); grade $\geq$2 sensory neuropathy persisted in 13 (6%) after chemoradiation therapy versus none after radiation therapy alone ($P < .001$). Other grade $\geq$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 chemoradiation therapy versus radiation therapy; 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 chemoradiation therapy).

Table 1 Characteristics of as-treated population by treatment group

Characteristics	CTRT n = 327	RT alone 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 (%).

Abbreviations: BSO = bilateral salpingo-oophorectomy; CTRT = chemoradiation therapy; FIGO = International Federation of Gynecology and Obstetrics; LND = lymph node dissection; RT = radiation therapy; TAH = total abdominal hysterectomy; TLH = total laparoscopic hysterectomy; WHO = World Health Organization.

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 (Fig. 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 chemoradiation therapy and radiation therapy, 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 (Fig. 2C). Trends for worse long-term pain and fatigue symptom scores after chemoradiation therapy 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 (Fig. E2). No long-term significant differences in social, cognitive, and emotional functioning were found between treatment groups or in comparison to the normative population (Fig. E1).

Among patients who had received chemoradiation therapy, 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 radiation therapy 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 Figure E3.

Symptom items

A complete overview of the proportion of patients reporting significant ("quite a bit" or "very much") symptoms is shown in supplementary Table E2. Patients treated with chemoradiation therapy reported more significant tingling or numbness throughout the 5-year follow-up period compared with patients who received radiation therapy alone. At 5 years, 32 (24%) patients treated with chemoradiation therapy reported significant tingling/numbness, in contrast to 9 (9%) treated with radiation therapy ($P = .002$). Likewise, 129 (62%) versus 66 (40%) patients had deteriorated in tingling/numbness compared with baseline ($P < .001$, Fig. 3 and Fig. E5A); no difference between patients with or without diabetes was found among patients treated with chemotherapy (Fig. E4C and E5B). A trend toward worse tingling/numbness in patients aged ≥70 years was found over time after chemoradiation therapy ($P = .016$) but not after radiation therapy ($P = .35$, Fig. A4 B). None of variables entered in the multivariate logistic regression model were statistically significant risk factors for tingling/numbness (data not shown).

Table 2 Adverse events reported by physicians using CTCAE v3.0 during treatment and at 3- and 5-year follow-up

	During treatment						At 3 years						At 5 years					
	Grade 2			Grade 3/4			Grade 2			Grade 3/4			Grade 2			Grade 3/4		
	CTRT n = 327	RT n = 333		CTRT n = 327	RT n = 333		CTRT n = 269	RT n = 277		CTRT n = 269	RT n = 277		CTRT n = 207	RT n = 193		CTRT n = 207	RT n = 193	
	n (%)	n (%)	*P*	n (%)	n (%)	*P*	n (%)	n (%)	*P*	n (%)	n (%)	*P*	n (%)	n (%)	*P*	n (%)	n (%)	*P*
Any	110 (34)	103 (31)	<.01	198 (61)	41 (12)	<.01	63 (23)	49 (18)	.04	21 (8)	16 (6)	.40	60 (29)	37 (19)	<.01	18 (9)	9 (5)	.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)	
Hypertension	19 (6)	12 (4)	.10	6 (2)	3 (1)	.34	15 (6)	17 (6)	.75	5 (2)	6 (2)	1.00	16 (8)	17 (9)	.63	4 (2)	5 (3)	.74
Lymphatics (edema)	7 (2)	4 (1)	.17	2 (1)	0 (0)	.25	3 (1)	1 (0)	.12	2 (1)	0 (0)	.24	5 (2)	2 (1)	.45	0 (0)	0 (0)	1.00
Gastrointestinal, any	145 (44)	79 (24)	<.01	47 (14)	18 (5)	<.01	11 (4)	17 (6)	.46	2 (1)	1 (0)	.62	15 (7)	10 (5)	.43	2 (1)	1 (1)	1.00
Diarrhea	103 (31)	68 (20)	<.01	35 (11)	14 (4)	<.01	4 (1)	8 (3)	.42	1 (0)	1 (0)	1.00	7 (3)	7 (4)	.80	2 (1)	0 (0)	.50
Ileus/obstruction	3 (1)	5 (2)	.77	2 (1)	2 (1)	1.00	0 (0)	0 (0)	.49	1 (0)	0 (0)	.49	2 (1)	1 (1)	.22	3 (1)	0 (0)	.25
Hematological, any	100 (31)	19 (6)	<.01	149 (46)	18 (5)	<.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)	<.01	109 (33)	17 (5)	<.01	1 (0)	0 (0)	.49	0 (0)	0 (0)	1.00	3 (1)	4 (2)	.72	0 (0)	0 (0)	1.00
Neuropathy, any	82 (25)	1 (0)	<.01	23 (7)	0 (0)	<.01	18 (7)	2 (1)	<.01	2 (1)	0 (0)	.24	13 (6)	0 (0)	<.01	1 (0)	0 (0)	1.00
Neuropathy, motor	13 (4)	1 (0)	<.01	4 (1)	0 (0)	.06	3 (1)	2 (1)	.44	1 (0)	0 (0)	.49	1 (0)	0 (0)	.50	1 (0)	0 (0)	1.00
Neuropathy, sensory	79 (24)	0 (0)	<.01	22 (7)	0 (0)	<.01	18 (7)	1 (0)	<.01	2 (1)	0 (0)	.24	12 (6)	0 (0)	<.01	1 (0)	0 (0)	1.00
Pain, any	101 (31)	23 (7)	<.01	31 (9)	4 (1)	<.01	17 (6)	15 (5)	.30	4 (1)	0 (0)	.06	15 (7)	6 (3)	.12	3 (1)	3 (2)	1.00
Arthralgia	52 (16)	2 (1)	<.01	10 (3)	0 (0)	<.01	2 (1)	5 (2)	.73	1 (0)	0 (0)	.49	9 (4)	4 (2)	.20	2 (1)	1 (1)	1.00
Muscle pain	52 (16)	1 (0)	<.01	9 (3)	0 (0)	<.01	3 (1)	0 (0)	.12	0 (0)	0 (0)	1.00	1 (0)	1 (1)	.61	0 (0)	1 (1)	.48
Back/pelvic/limbs	10 (3)	4 (1)	<.01	11 (3)	0 (0)	<.01	4 (1)	3 (1)	.50	1 (0)	0 (0)	.49	0 (0)	2 (1)	.11	0 (0)	1 (1)	.48
Abdomen/cramps	14 (4)	9 (3)	.28	4 (1)	4 (1)	1.00	5 (2)	1 (0)	.07	1 (0)	0 (0)	.49	2 (1)	0 (0)	.12	2 (1)	0 (0)	.50
Musculoskeletal (other)	2 (1)	2 (1)	.50	2 (1)	0 (0)	.50	1 (0)	0 (0)	.24	1 (0)	0 (0)	.49	0 (0)	1 (1)	1.00	0 (0)	0 (0)	1.00
Pulmonary, dyspnea	14 (4)	2 (1)	.25	5 (2)	0 (0)	.03	1 (0)	0 (0)	1.00	0 (0)	1 (0)	1.00	2 (1)	0 (0)	.50	0 (0)	0 (0)	1.00
Genitourinary																		
Incontinence	12 (4)	5 (2)	.06	1 (0)	0 (0)	.50	8 (3)	3 (1)	.09	1 (0)	0 (0)	.49	8 (4)	9 (5)	1.00	0 (0)	0 (0)	1.00
Urinary urgency	24 (7)	10 (3)	.01	2 (1)	2 (1)	1.00	7 (3)	5 (2)	.57	0 (0)	0 (0)	1.00	9 (4)	3 (2)	.14	0 (0)	0 (0)	1.00
Constitutional																		
Fatigue	69 (21)	7 (2)	<.01	10 (3)	0 (0)	<.01	1 (0)	0 (0)	.49	0 (0)	0 (0)	1.00	0 (0)	3 (2)	.11	0 (0)	0 (0)	1.00

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 $\leq$.01 were deemed significant.

Abbreviations: CTCAE v3.0 = Common Terminology Criteria for Adverse Events version 3.0; CTRT = combined chemotherapy and radiation therapy; RT = radiation therapy.

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

Sexual activity did not differ between the 2 treatment groups at 3 and 5 years (Table E2). 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 ($P < .001$; Fig. E6).

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 Figure E7.

Discussion

This long-term analysis of toxicity and HRQOL in the PORTEC-3 trial shows that combined adjuvant chemotherapy and radiation therapy for high-risk endometrial cancer may have a long-lasting clinically relevant negative impact on QOL, with a small long-term deterioration in physical and role functioning for the first 3 years after treatment compared with radiation therapy alone. Patients treated with chemoradiation therapy 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 chemoradiation therapy in endometrial cancer, with the strength of comparison to pelvic radiation therapy 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 chemoradiation therapy, with HRQOL showing "quite a bit" or "very much" tingling/numbness being reported by 24% at 5 years. The recovery

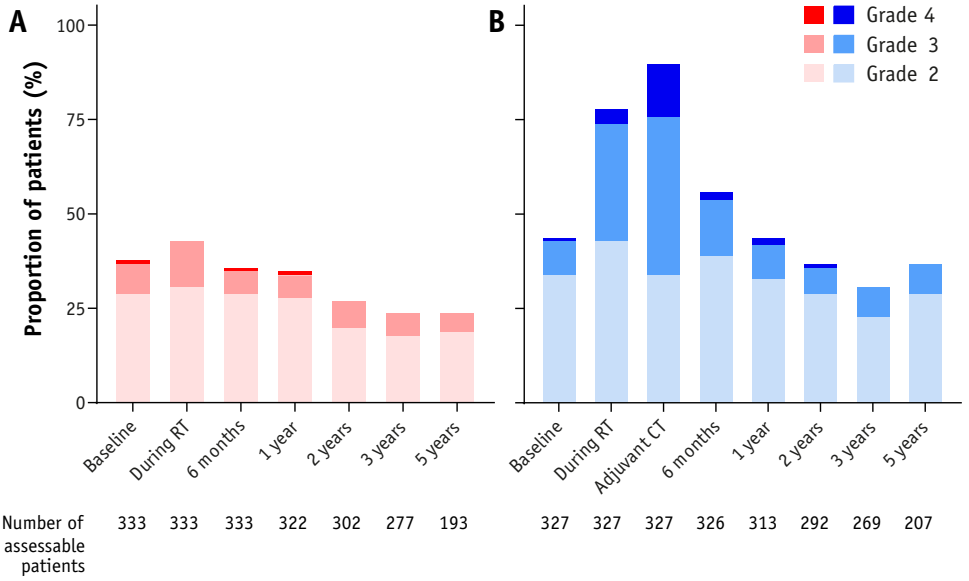

Fig. 1. Incidence of the maximum physician-reported adverse event grades per patient for each timepoint at baseline, during treatment, at 6-month follow-up, and at 1-, 2-, 3-, and 5-year follow-up after pelvic radiation therapy alone (A) and combined pelvic radiation therapy and chemotherapy (B).

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	
			After	Months						Time	Tx	Tx		
		Baseline	RT	6	12	36	60	Time	Tx	by Tx	at 3 y	at 5 y	60-69 yr	CS
EORTC-QLQ C30														
EORTC functioning scales														
Physical functioning	CTRT	81.3	76.0	72.6	79.9	79.4	81.4	<.001	<.001	<.001	<.001*	.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	<.001	<.001	<.001	.0007*	.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	<.001	.14	<.001	.33	.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	<.001	.0022	.035	.18	.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	<.001	<.001	<.001	.43	.72	88.1	T
	RT	80.1	78.7	88.1	89.9	87.2	91.2							T
Global health status/ QOL	CTRT	69.3	60.3	65.0	72.8	73.8	74.4	<.001	<.001	<.001	.37	.054	65.6	S
	RT	70.6	68.7	72.6	74.0	75.7	79.2							M
EORTC symptom scales														
Fatigue	CTRT	29.0	42.4	38.4	28.2	26.0	23.3	<.001	<.001	<.001	.015	.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	<.001	<.001	<.001	.67	.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	.008	.04	.09	.0075*	.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	<.001	.6	.0047	.56	.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	<.001	<.001	<.001	.0053*	.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	.059	.53	<.001	.83	.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	<.001	<.001	<.001	.0083	.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	<.001	<.001	<.001	<.001†	.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 health status/quality of life scale represent a better level of functioning. For the symptom scales, a higher score reflects a higher level of symptoms. *P* values <.01 for treatment comparison were deemed significant.

Abbreviations: CS = clinical significance at 5 years; CX = cervix; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire C30; CTRT = combined chemotherapy and radiation therapy; HRQOL = health-related quality of life; NM = medium difference; Norm = age-match normative data based on women aged 60 to 69 years across 13 European countries, Canada, and the United States[16]; OV = ovarian; *P* time = changes of quality-of-life scores over time; *P* Tx = difference between the 2 treatment groups; *P* Tx at 3 y = difference between the 2 treatment groups at 3 years; *P* Tx at 5 y = difference between the 2 treatment groups at 5 years; *P* time by Tx = difference between the 2 treatment groups over time; RT = radiation therapy; Tx = treatment; S = small difference; T = trivial difference.

* Clinically relevant small difference.

† Clinically relevant medium difference.

‡ Items included in the subscale are specified in supplementary Table E2.

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 radiation therapy 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.

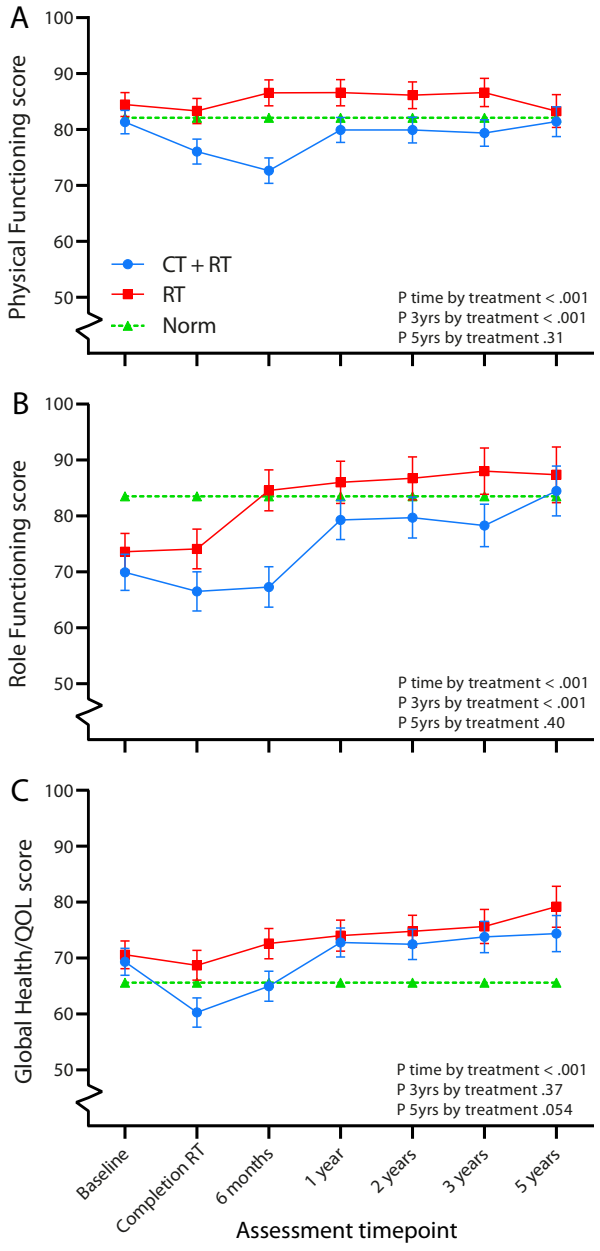

Fig. 2. Patient functioning on subscales from European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 for physical functioning (A), role functioning (B), and global health status/quality of life (C). A higher score indicates a higher level of functioning. Error bars show 95% confidence interval. *Abbreviations*: CT = chemotherapy; Norm = mean scores of age-match normative data based on women aged 60 to 69 years across 13 European countries, Canada, and the United States[16]; *P* time by treatment = difference between the 2 treatment groups over time; *P* 3yrs by treatment = difference between the 2 treatment groups at 3 years; *P* 5yrs by treatment = difference between the 2 treatment groups at 5 years; RT = radiation therapy; QOL = quality of life.

This comparison is relevant because patients with ovarian cancer are of similar age and had previous pelvic surgery without radiation therapy. 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 radiation therapy alone in women with high-intermediate and high-risk stage I-II endometrial cancer, also showed significantly higher CIPN rates in the chemotherapy arm (sensory neuropathy grade $\geq$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 chemoradiation therapy 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 (τ = 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.[6-8,10,11] 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 chemoradiation therapy 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, chemoradiation therapy 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

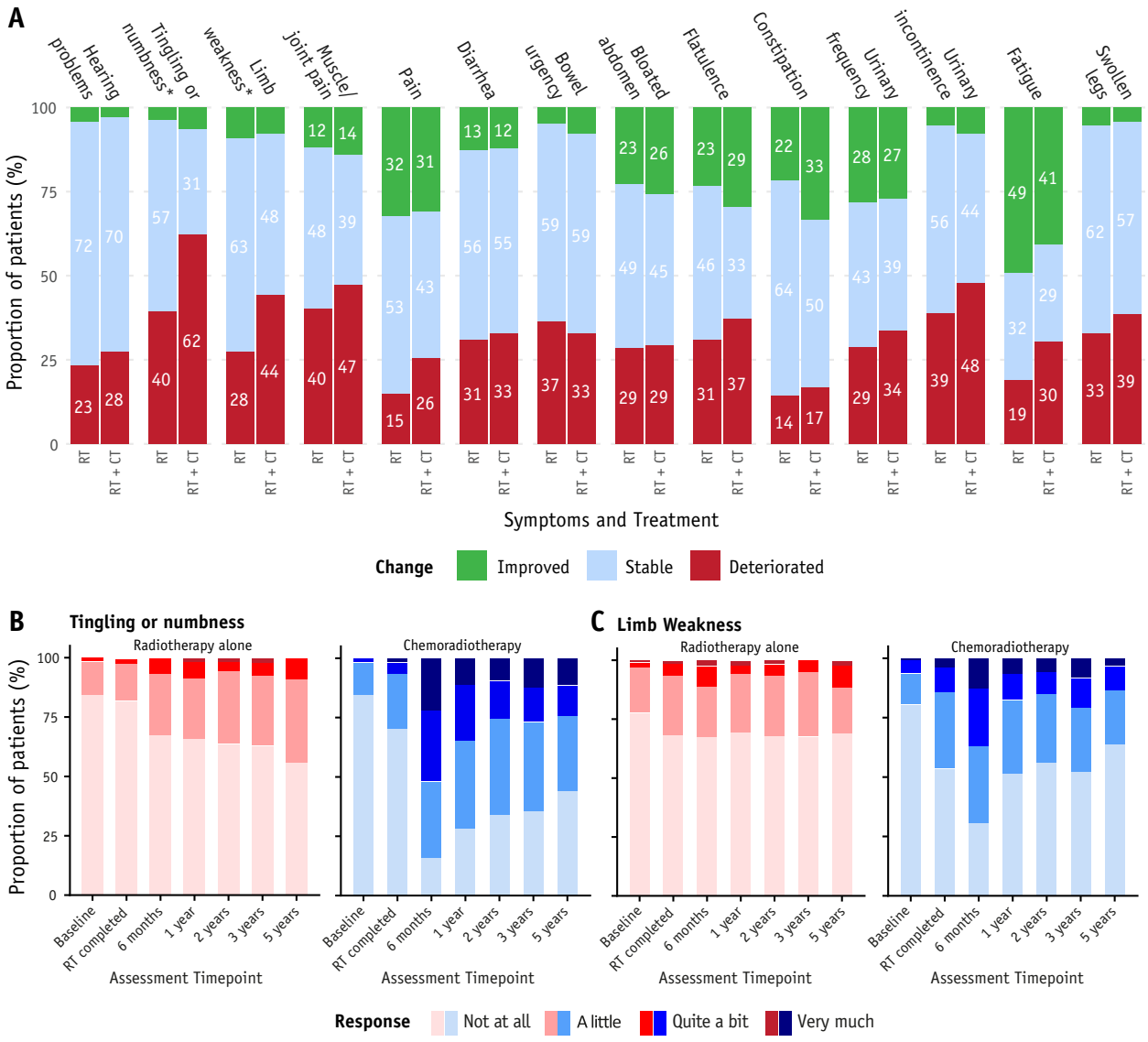

Fig. 3. Clinically relevant long-term changes compared with baseline in patient reported symptoms on European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, CX24, and OV28 on the individual patient level (A) and patient responses on single-items with significant change: tingling/numbness (B) and limb weakness (C). Long-term change is defined as the mean of 3- and 5-year scores compared with baseline score on the individual level. *P* values $\leq$.01 were deemed significant. **P* values show significance for deterioration versus improved or stable. *Abbreviations*: CT = chemotherapy; RT = radiation therapy; QOL = quality of life.

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 $\geq$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 chemoradiation therapy compared with radiation therapy. 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 radiation therapy 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 radiation therapy 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 radiation therapy and aging on the pelvic floor and bladder.[3,4]

The overall survival benefit of chemoradiation therapy compared with radiation therapy 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 chemoradiation therapy in those with *TP53*-mutated tumors, and chemotherapy might be omitted in *POLE* 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 radiation therapy on toxicity and QOL compared with radiation therapy 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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