Radiotherapy for endometrial cancer: improved patient selection, techniques and outcomes

Wortman, B.G.

CHAPTER 6

RADIOTHERAPY TECHNIQUES AND TREATMENT-RELATED TOXICITY IN THE PORTEC-3 TRIAL: COMPARISON OF THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY VERSUS INTENSITY-MODULATED RADIOTHERAPY

Bastiaan G. Wortman, Cathalijne C.B. Post, Melanie E. Powell, Pearly Khaw, Anthony Fyles, Romerai D'Amico, Christine Haie-Meder, Ina M. Jürgenliemk-Schulz, Mary McCormack, Viet Do, Dionyssios Katsaros, Paul Bessette, Marie Hélène Baron, Remi A. Nout, Karen Whitmarsh, Linda Mileshkin, Ludy C.H.W. Lutgens, Henry C. Kitchener, Susan Brooks, Hans W. Nijman, Eleftheria Astreinidou, Hein Putter, Carien L. Creutzberg, Stephanie M. de Boer.

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ABSTRACT

Purpose: Radiation therapy techniques have developed from 3-dimensional conformal radiation therapy (3DCRT) to intensity modulated radiation therapy (IMRT), with better sparing of the surrounding normal tissues. The current analysis aimed to investigate whether IMRT, compared to 3DCRT, resulted in fewer adverse events (AEs) and patient-reported symptoms in the randomized PORTEC-3 trial for high-risk endometrial cancer.

Methods and Materials: Data on AEs and patient-reported quality of life (QoL) of the PORTEC-3 trial were available for analysis. Physician-reported AEs were graded using Common Terminology Criteria for Adverse Events v3.0. QoL was assessed by the European Organisation for Research and Treatment of Cancer QLQC30, CX24, and OV28 questionnaires. Data were compared between 3DCRT and IMRT. A P value of $\leq .01$ was considered statistically significant due to the risk of multiple testing. For QoL, combined scores 1 to 2 ("not at all" and "a little") versus 3 to 4 ("quite a bit" and "very much") were compared between the techniques.

Results: Of 658 evaluable patients, 559 received 3DCRT and 99 IMRT. Median follow-up was 74.6 months. During treatment no significant differences were observed, with a trend for more grade $\geq$3 AEs, mostly hematologic and gastrointestinal, after 3DCRT (37.7% vs 26.3%, P = .03). During follow-up, 15.4% (vs 4%) had grade $\geq$2 diarrhea, and 26.1% (vs 13.1%) had grade $\geq$2 hematologic AEs after 3DCRT (vs IMRT) (both $P < .01$). Among 574 (87%) patients evaluable for QoL, 494 received 3DCRT and 80 IMRT. During treatment, 37.5% (vs 28.6%) reported diarrhea after 3DCRT (vs IMRT) (P = .125); 22.1% (versus 10.0%) bowel urgency (P = .039), and 18.2% and 8.6% abdominal cramps (P = .058). Other QoL scores showed no differences.

Conclusions: IMRT resulted in fewer grade $\geq$3 AEs during treatment and significantly lower rates of grade $\geq$2 diarrhea and hematologic AEs during follow-up. Trends toward fewer patient-reported bowel urgency and abdominal cramps were observed after IMRT compared to 3DCRT.

INTRODUCTION

Over the last decades, radiation therapy techniques have developed from parallel opposing fields or 2-dimensionally planned radiation therapy to 3- and 4-field techniques and to 3- dimensional conformal radiation therapy (3DCRT). More recent developments are 3- dimensional image guided intensity modulated radiation therapy (IMRT) and volumetric modulated arc radiation therapy (VMAT). With IMRT and VMAT, the radiation dose is delivered more conformally to the target volume and the dose to the adjacent organs at risk (OARs) is reduced, compared to 3DCRT, without compromising clinical outcome.[1-6] With the introduction of more advanced radiation therapy techniques, it is expected that treatment-related adverse events (AEs) for pelvic radiation therapy can be reduced.

Multiple retrospective studies and 2 prospective randomized trials have shown that intensity modulated techniques significantly reduce treatment-related acute and late AEs and patient-reported symptoms in women with endometrial or cervical cancer.[5-12] However, limitations of most studies were small numbers of patients, retrospective data collection, limited follow-up, or lack of data on patient-reported symptoms.

The randomized PORTEC-3 trial investigated radiation therapy versus chemoradiation therapy for women with high-risk endometrial cancer (EC) and showed that radiation therapy combined with concurrent and adjuvant chemotherapy improved overall and failure-free survival.[13] Analyses of acute AEs showed that pelvic radiation therapy was associated with mostly gastrointestinal acute AEs of mild to moderate severity and that the addition of chemotherapy resulted in added hematologic and neurologic AEs.[14,15] Within the PORTEC-3 trial, 68.5% (94.2% chemoradiation therapy vs 43.2% radiation therapy alone) had any grade ≥2 AEs during treatment, and 44.3% and 43.8% of all patients experienced grade ≥2 gastrointestinal and hematologic AEs, respectively. Persistent grade ≥2 AEs, up to 5 years after treatment, were observed for 31%, with 7.3% gastrointestinal and 2.5% hematologic AEs.[15,16]

In the PORTEC-3 trial, the standard radiation technique used at the time was 3DCRT, but IMRT was allowed if standard for the center and with adequate quality assurance (QA). The aim of the current study was to investigate whether use of IMRT in the PORTEC-3 trial was associated with reduced physician-reported AEs and fewer patient-reported symptoms.

METHODS AND MATERIALS

Study design and patient selection of the PORTEC-3 trial

The international, randomized PORTEC-3 trial was designed to investigate the benefit of external beam radiation therapy with concurrent and adjuvant chemotherapy (chemoradiation therapy)

compared to radiation therapy alone in women with high-risk EC. Inclusion criteria for the trial were endometrioid-type EC, Federation of Gynecology and Obstetrics 2009 stage I, grade 3, with myometrial invasion and lymphovascular space invasion; stage II; stage IIIA; stage IIIB (parametrial invasion only) or stage IIIC; and serous or clear cell type EC stage IA (with invasion) to III. Primary endpoints of the trial were overall survival and failure-free survival; secondary endpoints included physician-reported AEs, patient-reported quality of life (QoL), and pelvic or distant relapse. More detailed information on patient selection, treatment, and outcomes has been reported in previous publications.[13, 15, 16]

Procedures

All women underwent surgery that consisted of total abdominal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy, with or without lymph node dissection. After surgery, they were randomized 1:1 to either pelvic external beam radiation therapy alone or concurrent chemotherapy and pelvic radiation therapy, administered with a total dose of 45.0 to 50.4 Gy with a recommended dose of 48.6 Gy in 1.8 Gy daily fractions 5 times a week. A vaginal brachytherapy boost was indicated in case of cervical stromal involvement. The clinical target volume for external beam radiation therapy consisted of the proximal half of the vagina; the parametrial tissues; pelvic lymph nodes; and internal, external, and common iliac lymph node regions up to the upper level of S1. It was extended in case lymph nodes were involved. The planning target volume consisted of the CTV with a 7 to 10 mm margin. Standard technique was computed tomography–based 3DCRT (four-field "box" technique with or without supplementary fields or segments), according to the ICRU-50 recommendations. IMRT, with similar margins, was allowed when centers had sufficient clinical experience with pelvic IMRT and had arranged adequate local QA procedures as dose verification and daily cone-beam computed tomography. Radiation therapy QA was initially not included in the trial, but was added later by the Trans-Tasman Radiation Oncology Group. The QA procedure for centers of the Australia and New Zealand Gynaecologic Oncology Group consisted of a benchmarking exercise before participation in the trial and regular QA thereafter; for international sites, an independent retrospective review of a single radiation therapy plan of each participating center was conducted.[17]

Treatment should preferably start within 4 to 6 weeks, but no later than 8 weeks, from surgery. In the chemoradiation therapy arm, patients received 2 cycles of cisplatin the first and fourth week of radiation therapy, and 4 cycles of 3-weekly carboplatin and paclitaxel after completion of radiation therapy.

Adverse events and quality of life assessment

Physician-reported AEs were assessed by the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 at baseline (after surgery), after completion of the radiation therapy, at each

cycle of adjuvant chemotherapy, at a 6-month interval until 5 years, and at 7 and 10 years from randomization. For the QoL assessment, a questionnaire including the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) version 3.0, the cervix module (CX-24), and subscales for neuropathy and chemotherapy symptoms from the ovarian module (OV-28) were used.[18] For the single items, symptom scores between 1 and 4 were recorded, with 1 being no symptoms ("not at all"), 2 "a little," 3 "quite a bit," and 4 "very much" for each symptom.

Questionnaires were filled out at baseline after surgery, after completion of radiation therapy, every 6 months until 2 years, and thereafter at 3 and 5 years from randomization.[15, 16]

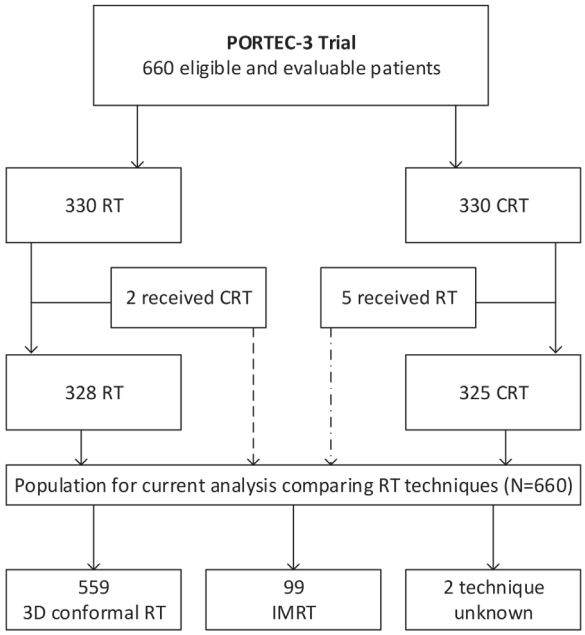
Statistical design

Statistical analyses were performed with SPSS, version 25.0 (SPSS, Inc., Chicago, IL). All patients were evaluable for analysis of physician-reported AEs. Patients who filled in the baseline and at least 1 follow-up questionnaire were included in the QoL analysis. Patients did not receive further QoL questionnaires after being diagnosed with a recurrence; however, all data, up to the date of a recurrence, were included in the analysis.

To compare patient and tumor characteristics between the 2 radiation techniques $\chi 2$ statistics or Fisher's exact test for categorical variables and t test for continuous variables were used (significance P value $<.05$). Physician-reported AEs were calculated at each timepoint (using the maximum grade scored) and compared between the radiation therapy techniques by the Fisher exact test.

The timepoint "during treatment" consisted of all AE forms related to radiation therapy and concurrent and adjuvant chemotherapy and the timepoint "during follow-up" of all AE forms collected during the entire follow-up period. For these timepoints, the maximum grade was used as a summary of toxicity. QoL analysis was done according to the EORTC Quality of Life Group guidelines.[18] 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), technique, and their interaction as fixed effects. Single items were compared by using generalized mixed models binary logistic regression with the same random and fixed effects as the linear mixed model, with combined scores 1 to 2 ("not at all" and "a little") and 3 to 4 ("quite a bit" and "very much"). Missing data were handled as missing at random. A P value of $\leq .01$ was considered statistically significant to prevent false-positive results due to multiple testing.

Figure 1. Flowchart of the PORTEC-3 trial.



RT: Radiotherapy; CRT: Chemoradiotherapy; IMRT: Intensity-modulated radiotherapy.

RESULTS

Study population

Between September 15, 2006, and December 20, 2013, 660 eligible and evaluable patients were included in the PORTEC-3 trial. Of these patients, 333 received radiation therapy and 327 received chemoradiation therapy; 559 (85.0%) received 3DCRT; 99 (15.0%) patients received IMRT; and for 2 patients, the type of technique was unknown (Fig. 1). 3DCRT consisted of 3-field, 4-field, or multiple-field radiation therapy techniques. IMRT was used in 42 of 103 participating centers and typically consisted of 7 static fields with multiple segments (Fig. E1). Median follow-up at the time of analysis was 74.6 months. Patient characteristics by initial treatment arm and technique are displayed in Table 1and showed no significant differences. IMRT and 3DCRT were used equally in both initial treatment arms (Table 1). Radiation therapy target areas (pelvic vs pelvic and paraortic region) did not differ significantly between the 2 techniques, with only 38 patients receiving paraortic radiation therapy. Of all patients, 574 (87.0%) patients were evaluable for QoL, of whom 493 (85.9%) received 3DCRT and 80 (13.9%) IMRT; for 1 patient, the technique was unknown (0.2%). The completion rate of the QoL questionnaire was 89.4% at 3 years and 62.8% at 5 years.

Physician-reported adverse events

At baseline, no significant differences in frequency and grades of AEs were observed between the radiation therapy techniques. Specifically, 226 of 559 patients (40.4%) and 41 of 99 (41.4%) patients had any grade ≥2 AE at baseline (after surgery); 57 of 559 (10.2%) and 4 of 99 (4.0%) any grade ≥3 AE (P = .92 and P = .06, respectively).

The most frequent AEs during treatment were gastrointestinal (43.6%), hematologic (43.3%), and pain (24.0%). No significant differences were found between the radiation therapy techniques, and a trend for more grade ≥3 AEs was observed with 3DCRT (37.7% vs 26.3% for IMRT, P = 0.03) (see Table 2 and Fig. 2). At 6 months, 274 of 560 (48.9%) patients who had been treated with 3DCRT had any grade ≥2 AE versus 29 of 97 (29.9%) of those who had received IMRT (P < .01). Grade ≥2 hematologic AEs were reported for 104 of 560 (18.6%) and 7 of 97 (7.2%) patients (P < .01). During follow-up, 443 of 559 (79.2%) versus 67 of 99 (67.7%) patients had any grade ≥2 AE (P = .01), of whom 78 (13.9%) versus 4 (4.0%) had grade ≥2 diarrhea and 143 (25.6%) versus 13 (13.1%) any grade ≥2 hematologic AE, respectively (both P < .01) (Table E1). A total of 176 (31.5%) versus 21 (21.2%) patients had any grade ≥3 AE during follow-up (P = .04) (Table E1). At 1, 2, and 3 years, no significant differences were recorded. At 5 years, significantly more grade ≥2 AEs were observed after 3DCRT (33.5% vs 14.6%, P < .01), but toxicity data were only available for 60% of patients at this time point. No significant differences were recorded for genitourinary AEs.

Table 1. Patient characteristics.

	PORTEC-3 population by technique (n = 658)			PORTEC-3 population by arm (n = 660)	
	IMRT (n = 99)	Conformal RT (n = 559)	*P value*	CRT (n = 327)	RT (n = 333)
Age at randomization, y					
Median	62.2 (56.1-68.1)	62.9 (56.5-68.0)	.24	61.9 (55.9-68.1)	62.5 (56.5-68.0)
<60	34 (34.3%)	232 (41.5%)	-	127 (38.8%)	141 (42.3%)
60-69	48 (48.5%)	224 (40.1%)	-	142 (43.4%)	130 (39.0%)
≥70	17 (17.2%)	103 (18.4%)	-	58 (17.7%)	62 (18.6%)
WHO					
0-1	95 (96,9%)	550 (98.7%)	0.18	320 (98.5%)	327 (98.5%)
2	3 (3.1%)	7 (1.3%)	-	5 (1.5%)	5 (1.5%)
Unknown	1	2		2	1
Comorbidity					
Diabetes	8 (8.1%)	73 (13.1%)	.33	45 (13.8%)	36 (10.8%)
Hypertension	36 (36.4%)	184 (33.0%)	.49	115 (35.2%)	105 (31.6%)
Cardiovascular	10 (10.2%)	39 (7.0%)	.50	29 (9.0%)	20 (6.0%)
FIGO					
Ia	10 (10.1%)	67 (12.0%)	.30	39 (11.9%)	39 (11.7%)
Ib	13 (13.1%)	103 (18.4%)	-	58 (17.7%)	59 (17.7%)
II	28 (28.3%)	142 (25.4%)	-	79 (24.2%)	91 (27.3%)
III	48 (48.5%)	247 (44.2%)	-	151 (46.2%)	144 (43.2%)
Histology					
Endometrioid	72 (72.7%)	398 (71.2%)	.27	234 (70.9%)	237 (71.8%)
Serous	13 (13.1%)	92 (16.5%)	-	53 (16.1%)	52 (15.8%)
Clear cell	8 (8.1%)	53 (9.5%)	-	29 (8.7%)	33 (10.0%)
Other	6 (6.1%)	16 (2.9%)	-	14 (4.3%)	8 (2.4%)
Type of surgery					
TAH-BSO	29 (29.3%)	164 (29.3%)	.96	96 (29.4%)	98 (29.4%)
TAH-BSO with LND/ full staging	39 (39.4%)	234 (41.9%)	-	140 (42.8%)	133 (39.9%)
TLH-BSO	14 (14.1%)	72 (12.9%)	-	44 (13.5%)	43 (12.9%)
TLH-BSO with LND/full staging	17 (17.2%)	89 (15.9%)	-	47 (14.4%)	59 (17.7%)
Treatment					
Chemoradiation arm	53 (53.5%)	273 (48.8%)	0.69	327 (100%)	-
Radiation therapy arm	46 (46.5%)	286 (51.2%)	-	-	333 (100%)
Brachytherapy boost	48 (48.5%)	261 (46.7%)	0.73	149 (45.6%)	160 (48.0%)
Radiation therapy technique					
IMRT	99 (100%)	-	-	53 (16.2%)	46 (13.8%)
Conformal RT	-	559 (100%)	-	273 (83.5%)	286 (85.9%)

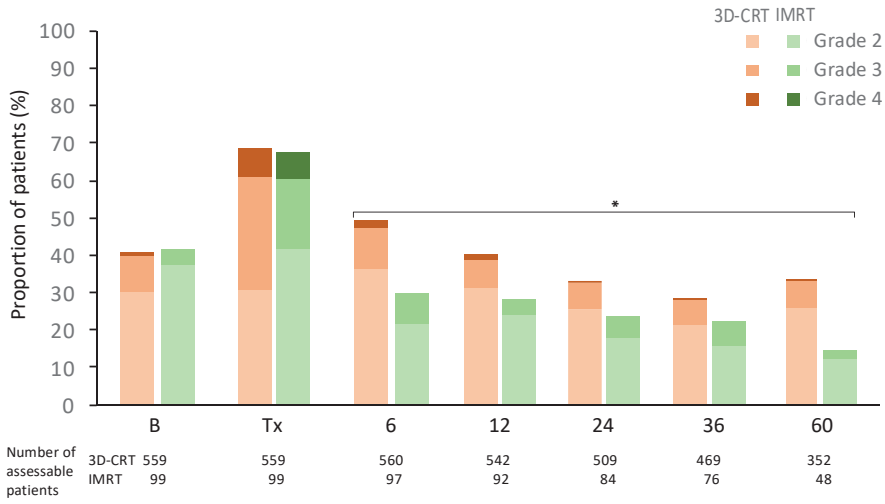
Abbreviations: CRT = chemoradiation therapy; IMRT = intensity modulated radiation therapy; LND = lymph node dissection; RT = radiation therapy; TAH-BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy; TLH = total laparoscopic hysterectomy.

Table 2. Physician-reported toxicity during treatment, at 6 months and at 3 years by radiotherapy technique.

	During treatment						At 6 months						At 3 years					
	Grade 2		P*	Grade 3-4		P	Grade 2		P*	Grade 3-4		P	Grade 2		P*	Grade 3-4		P
	IMRT (n = 99)	3DCRT (n = 559)		IMRT (n = 99)	3DCRT (n = 559)		IMRT (n = 97)	3DCRT (n = 560)		IMRT (n = 97)	3DCRT (n = 560)		IMRT (n = 76)	3DCRT (n = 469)		IMRT (n = 76)	3DCRT (n = 469)	
Any	41 (41%)	172 (31%)	0.91	26 (26%)	211 (38%)	0.03	21 (22%)	203 (36%)	<0.01	8 (8%)	71 (13%)	.24	12 (16%)	99 (21%)	0.33	5 (7%)	33 (7%)	1.00
Any grade 3	-	-		19 (19%)	168 (30%)		-	-		8 (8%)	62 (11%)		-	-		5 (7%)	32 (7%)	
Any grade 4	-	-		7 (7%)	43 (8%)		-	-		0 (0%)	9 (2%)		-	-		0 (0%)	1 (<1%)	
Gastrointestinal, any	38 (38%)	185 (33%)	1.00	5 (5%)	59 (11%)	.09	5 (5%)	32 (6%)	0.55	1 (1%)	15 (3%)	.49	5 (7%)	23 (5%)	0.42	1 (1%)	2 (<1%)	.36
Diarrhea	29 (29%)	141 (25%)	0.91	3 (3%)	45 (8%)	.09	1 (1%)	18 (3%)	0.23	0 (0%)	3 (1%)	1.00	2 (3%)	10 (2%)	1.00	0 (0%)	2 (<1%)	1.00
Nausea	14 (14%)	78 (14%)	1.00	1 (1%)	10 (2%)	1.00	2 (2%)	10 (2%)	1.00	0 (0%)	7 (1%)		0 (0%)	1 (<1%)	1.00	0 (0%)	0 (0%)	1.00
Vomiting	5 (5%)	35 (6%)	0.83	1 (1%)	4 (1%)	.56	1 (1%)	12 (2%)	0.49	0 (0%)	3 (1%)		0 (0%)	1 (<1%)	1.00	0 (0%)	0 (0%)	1.00
Constipation	3 (3%)	35 (6%)	0.25	0 (0%)	1 (<1%)	1.00	2 (2%)	9 (2%)	1.00	0 (0%)	3 (1%)	1.00	1 (1%)	5 (1%)	0.60	0 (0%)	0 (0%)	1.00
Ileus/obstruction	2 (2%)	6 (1%)	0.40	1 (1%)	3 (1%)	.48	0 (0%)	2 (<1%)	0.49	1 (1%)	14 (3%)	.71	0 (0%)	0 (0%)	0.14	1 (1%)	0 (0%)	.14
Genitourinary																		
Dysuria	8 (8%)	24 (4%)	1.00	1 (1%)	0 (0%)	.15	0 (0%)	8 (1%)	0.61	0 (0%)	0 (0%)	1.00	1 (1%)	3 (1%)	0.45	0 (0%)	0 (0%)	1.00
Urinary frequency/ urgency	5 (5%)	29 (5%)	0.82	0 (0%)	4 (1%)	1.00	1 (1%)	10 (2%)	1.00	0 (0%)	0 (0%)	1.00	0 (0%)	12 (3%)	0.39	0 (0%)	0 (0%)	1.00
Incontinence	2 (2%)	15 (3%)	1.00	0 (0%)	1 (<1%)	1.00	1 (1%)	12 (2%)	0.71	0 (0%)	1 (<1%)	1.00	0 (0%)	11 (2%)	0.39	0 (0%)	1 (0%)	1.00
Pain, any	19 (19%)	104 (19%)	1.00	5 (5%)	30 (5%)	1.00	6 (6%)	57 (10%)	0.22	1 (1%)	9 (2%)	1.00	6 (8%)	26 (6%)	0.62	0 (0%)	4 (1%)	1.00
Muscle pain	8 (8%)	45 (8%)	1.00	1 (1%)	8 (1%)	1.00	0 (0%)	6 (1%)	0.60	0 (0%)	0 (0%)	1.00	0 (0%)	3 (1%)	1.00	0 (0%)	0 (0%)	1.00
Arthralgia	7 (7%)	46 (8%)	0.71	1 (1%)	9 (2%)	1.00	1 (1%)	13 (2%)	1.00	1 (1%)	0 (0%)	.15	1 (1%)	6 (1%)	1.00	0 (0%)	1 (<1%)	1.00
Back/pelvic/limbs	4 (4%)	10 (2%)	0.57	1 (1%)	10 (2%)	1.00	2 (2%)	17 (3%)	1.00	1 (1%)	2 (<1%)	.38	1 (1%)	6 (1%)	1.00	0 (0%)	1 (<1%)	1.00
Abdomen/cramps	5 (5%)	18 (3%)	0.61	1 (1%)	7 (1%)	1.00	3 (3%)	11 (2%)	0.75	0 (0%)	5 (1%)	1.00	3 (4%)	3 (1%)	0.06	0 (0%)	1 (<1%)	1.00
Musculoskeletal	1 (1%)	3 (1%)	1.00	0 (0%)	2 (<1%)	1.00	0 (0%)	2 (<1%)	1.00	0 (0%)	0 (0%)	1.00	0 (0%)	1 (<1%)	1.00	0 (0%)	1 (<1%)	1.00
Fatigue	16 (16%)	59 (11%)	0.33	0 (0%)	10 (2%)	.37	2 (2%)	10 (2%)	0.45	1 (1%)	1 (<1%)	.27	1 (1%)	0 (0%)	0.14	0 (0%)	0 (0%)	1.00
Neuropathy, any	12 (12%)	70 (13%)	0.46	1 (1%)	22 (4%)	0.23	3 (3%)	40 (7%)	0.55	3 (3%)	7 (1%)	.17	2 (3%)	17 (4%)	1.00	1 (1%)	2 (<1%)	.36
Motor	0 (0%)	14 (3%)	0.09	0 (0%)	4 (1%)	1.00	0 (0%)	8 (1%)	0.70	1 (1%)	4 (1%)	.55	2 (3%)	3 (1%)	0.20	0 (0%)	1 (<1%)	1.00
Sensory	12 (12%)	66 (12%)	0.65	1 (1%)	21 (4%)	0.23	3 (3%)	38 (7%)	0.52	2 (2%)	4 (1%)	.22	2 (3%)	16 (3%)	1.00	1 (1%)	2 (<1%)	.36
Hematological, any	16 (16%)	103 (18%)	0.23	21 (21%)	145 (26%)	0.38	2 (2%)	79 (14%)	<0.01	5 (5%)	25 (4%)	.79	0 (0%)	6 (1%)	1.00	1 (1%)	2 (<1%)	.36
Lymphatics (edema)	1 (1%)	10 (2%)	0.70	0 (0%)	2 (<1%)	1.00	4 (4%)	7 (1%)	0.09	0 (0%)	1 (<1%)	1.00	0 (0%)	4 (1%)	1.00	0 (0%)	2 (<1%)	1.00
Hypertension	4 (4%)	27 (5%)	0.49	0 (0%)	9 (2%)	0.37	4 (4%)	29 (5%)	0.38	0 (0%)	10 (2%)	.37	3 (4%)	29 (6%)	0.25	0 (0%)	11 (2%)	.38

Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; RT = radiation therapy.
The maximum grade per patient per adverse event is shown.
* *P* values show significance for grade 2-4 adverse events.
Events at 1 and 2 years were similar to 3 years and therefore are not shown.

Figure 2. Incidence of the maximum physician-reported adverse event grades per patient for each timepoint in months at baseline, during and after 3-dimensional conformal radiation therapy and intensity modulated radiation therapy.

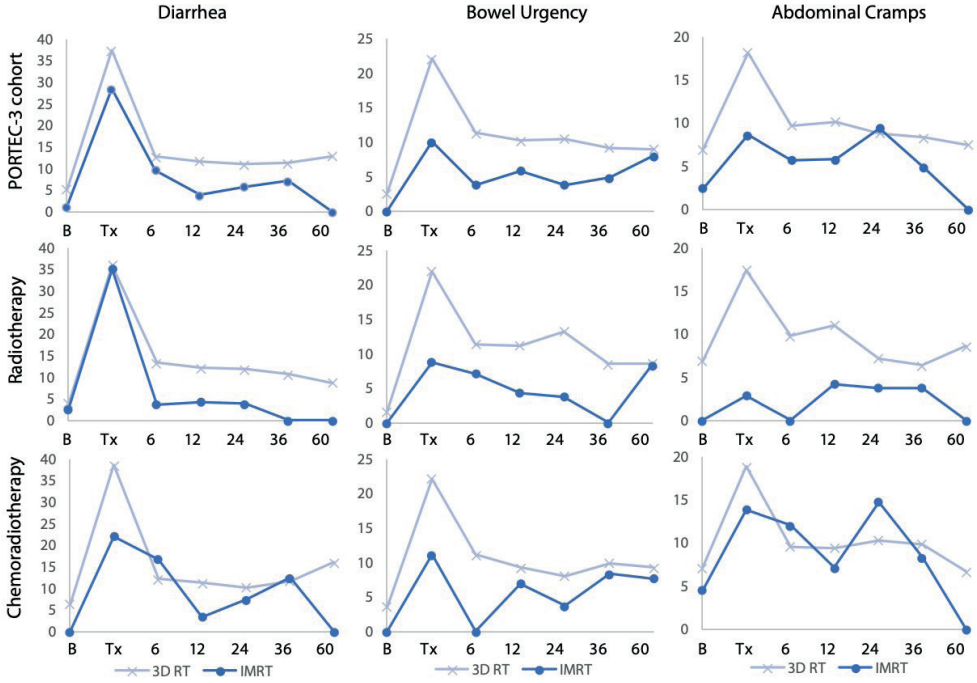


Abbreviations: B = baseline; 3DRT = 3-dimensional radiation therapy; IMRT = intensity modulated radiation therapy; Tx = during treatment (time in months) * significant difference.

Patient-reported symptoms on the QoL questionnaires

During treatment, the most common symptoms scored as “quite a bit” or “very much” were urinary frequency (40.3%), diarrhea (33.1%), and fatigue (32.1%), without significant differences between the radiation therapy techniques (Table 3). Trends were observed for more bowel urgency and abdominal cramps during treatment for those who received 3DCRT (22.1% vs 10.0% for IMRT [P = .039] and 18.2% vs 8.6% [P = .058]) (Fig. 3). Among genitourinary symptoms, urinary frequency differed significantly over time, without significant differences between the techniques at fixed timepoints (Table 3) (Fig. E2). At 6 months, 12.7% versus 9.6%, 11.3% versus 3.8%, and 9.7% versus 5.7% of patients (P = .670, P = .170, and P = .316, respectively) who had been treated with 3DCRT versus IMRT reported “quite a bit” to “very much” diarrhea, bowel urgency, and abdominal cramps. For patients who received radiation therapy only, these percentages were 13.3% versus 3.6%, 22.0% versus 8.8%, and 17.5% versus 2.9% (P = .158, P = .390, and P = .996, respectively). At 1, 2, and 3 years, no significant differences were observed in gastrointestinal and genitourinary symptoms between the 2 techniques. Development over time of other symptoms, such as lower back and muscle and joint pain, differed significantly by technique, without differences between the techniques at fixed timepoints (Table 3 and Fig. E2). Vaginal and sexual symptoms did not differ between the 2 techniques. Physical functional scales did not differ between 3DCRT and IMRT.

Figure 3. Percentage of patients who reported "quite a bit" or "very much" of diarrhea, bowel urgency or abdominal cramps in the total PORTEC-3 cohort, during and after radiation therapy only and after chemoradiation therapy.



Abbreviations: B = baseline; 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; Tx = during treatment (time in months).

DISCUSSION

This analysis of radiation therapy techniques in the PORTEC-3 trial showed that IMRT, compared to 3DCRT, was associated with lower rates of grade ≥3 AEs, mostly gastrointestinal and hematologic, during treatment. Furthermore, IMRT significantly reduced grade ≥2 AEs and grade ≥2 diarrhea and hematologic AEs during follow-up. Analysis of patient-reported QoL showed trends toward a reduced symptom burden with lower scores for diarrhea, bowel urgency, and abdominal cramps after IMRT versus 3DCRT. These findings support the rationale that women with high-risk EC should be treated with modern techniques such as IMRT or VMAT.

Table 3. Percentage of patients who reported symptoms scored as "quite a bit" or "very much" by radiation technique.

									P value						
		Baseline	Tx	6 mo	12 mo	24 mo	36 mo	60 mo	Technique	Time	Techn × time	Tx	6 mo	3 y	5 y
Gastro-intestinal															
Diarrhea	IMRT	1.2	28.6	9.6	3.8	5.7	7.1	0.0	.385	<.001	.018	.125	.670	.344	.891
	3DCRT	5.2	37.5	12.7	11.7	11.0	11.2	12.9							
Rectal bleeding	IMRT	0.0	1.4	0.0	0.0	1.9	0.0	0.0	.999	.999	.999	.666	.999	.999	.999
	3DCRT	0.6	0.7	1.0	0.3	1.4	0.3	0.5							
Bowel urgency	IMRT	0.0	10.0	3.8	5.8	3.8	4.8	8.0	.535	.812	.011	.039	0.170	0.390	0.731
	3DCRT	2.6	22.1	11.3	10.2	10.5	9.2	9.0							
Abdominal cramps	IMRT	2.4	8.6	5.7	5.8	9.4	4.8	0.0	.498	.543	.965	.058	0.316	0.311	0.933
	3DCRT	7.0	18.2	9.7	10.2	8.8	8.3	7.5							
Flatulence	IMRT	10.7	13.2	30.2	24.5	9.4	19.0	12.5	.149	.043	.075	.152	0.244	0.886	0.708
	3DCRT	15.3	20.6	20.8	20.7	21.7	18.9	19.6							
Genitourinary															
Urinary frequency	IMRT	26.2	44.3	20.8	22.6	19.2	28.6	8.0	.369	.001	.283	.285	0.912	0.594	0.028
	3DCRT	21.9	36.3	19.5	23.0	18.8	21.7	27.5							
Dysuria	IMRT	3.6	15.7	1.9	1.9	3.8	4.8	0.0	.873	.031	.543	.872	0.572	0.304	0.937
	3DCRT	5.2	16.1	2.6	2.6	1.4	1.9	1.9							
Urinary incontinence	IMRT	1.2	2.9	7.5	7.5	7.5	14.3	0.0	.980	.389	.001	.486	0.913	0.829	0.990
	3DCRT	3.8	6.0	6.5	8.4	9.6	12.8	11.8							
Difficulty emptying bladder	IMRT	6.0	5.7	3.8	3.8	5.7	7.1	4.0	.960	.993	.996	.759	0.384	0.490	0.781
	3DCRT	3.4	4.7	2.4	2.3	2.5	3.5	3.8							
Vaginal bleeding	IMRT	1.2	0.0	1.9	0.0	1.9	0.0	0.0	.995	.999	.999	.997	0.765	0.998	0.998
	3DCRT	0.8	1.0	1.3	1.0	0.3	0.3	0.5							
Vaginal dryness*	IMRT	0.0	21.4	16.7	20.0	16.7	33.3	25.0	.999	.984	.204	.837	0.772	0.946	0.808
	3DCRT	8.8	22.5	23.4	27.7	28.4	27.7	26.9							
Pain during sex*	IMRT	0.0	28.6	11.1	15.0	16.7	26.7	12.5	.998	.949	.246	.671	0.543	0.874	0.796
	3DCRT	2.8	21.2	17.5	16.4	17.9	18.8	19.7							
Other symptoms of interest															
Fatigue	IMRT	12.3	29.0	26.4	15.1	14.8	17.1	20.0	.767	.134	.687	.259	0.675	0.884	0.257
	3DCRT	17.9	35.1	23.8	17.4	18.2	18.9	12.9							
Nausea	IMRT	3.6	8.6	3.8	0.0	1.9	2.4	0.0	.966	.891	.977	.187	0.700	0.947	0.997
	3DCRT	3.4	14.6	5.4	3.8	3.9	2.9	4.7							
Vomiting	IMRT	1.2	1.4	0.0	0.0	1.9	0.0	0.0	.997	.999	.981	.566	0.998	0.998	0.999
	3DCRT	0.2	3.0	3.1	1.3	0.8	0.3	1.4							
Pain	IMRT	13.1	10.0	19.2	5.7	13.5	19.0	8.0	.380	.249	.375	.201	0.379	0.248	0.640
	3DCRT	10.0	14.1	16.6	14.8	13.5	13.1	10.4							
Lower back pain	IMRT	9.5	10.0	7.5	17.3	13.2	14.3	4.2	.424	.191	.001	.948	0.078	0.314	0.109
	3DCRT	10.0	9.0	17.4	16.5	18.3	19.4	19.6							
Muscle or joint pain	IMRT	6.0	22.1	32.7	29.4	24.0	28.6	13.6	.289	<.001	<.001	.129	0.492	0.110	0.900
	3DCRT	8.8	14.2	29.3	20.6	20.6	22.2	21.2							
Tingling or numbness	IMRT	0.0	1.4	22.6	26.9	11.3	16.7	8.0	.659	.040	<.001	.295	0.204	0.891	0.559
	3DCRT	1.8	5.0	30.8	22.4	16.7	18.4	18.5							

Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; Tx = during treatment.

* Only answered when sexually active.

Our study showed that IMRT resulted in fewer grade ≥3 AEs, mostly gastrointestinal, during treatment, which is consistent with findings of similar studies on the effect of IMRT for cervical cancer or EC on treatment-related acute AEs.[4, 5, 19] Aside from fewer grade ≥3 AEs, others reported fewer grade ≥2 gastrointestinal AEs during and directly after IMRT, but this could not be confirmed in the present study.[5, 9] We observed significantly fewer grade ≥2 AEs during follow-up, mainly diarrhea and hematologic AEs, for women who received IMRT compared to 3DCRT, even up to 5 years, which is in line with other reports on the long-term effects of IMRT versus 3DCRT for women with gynecologic malignancies.[5, 6, 10]

Patient-reported QoL did not differ significantly between the 2 radiation therapy techniques, although there were clear trends for fewer bowel symptoms such as cramps and urgency during and after IMRT. These trends seemed more obvious for women who received radiation therapy alone, but there was a slight imbalance at baseline in bowel symptoms favoring IMRT that could have influenced these trends. For women who received chemoradiation therapy a reduction of bowel symptoms was observed during treatment, but not during follow-up. Because 50% of patients in the PORTEC-3 trial received radiation therapy and 50% chemoradiation therapy and only 15.0% received IMRT, the number of patients was limited, and we were not able to draw conclusions on the interaction of RT techniques and treatment received. The results of the RTOG 1203 trial, which randomized women with endometrial or cervical cancer to either 3DCRT versus IMRT, showed significantly fewer bowel symptoms during and directly after IMRT compared to 3DCRT for women with endometrial and cervical cancer.[11, 12] This study used different QoL questionnaires compared to those in the present study, which makes it difficult to directly compare to our findings. Nevertheless, diarrhea, bowel urgency, and abdominal cramps seem to be prominent symptoms that were shown to be reduced with IMRT compared to 3DCRT in both the RTOG 1203 and the present study.

The lower rate of physician-reported AEs with IMRT for gynecologic malignancies has been related to reduced radiation doses to the small bowel, bladder, and rectum.[4, 5, 9, 10] Importantly, IMRT additionally spares pelvic bone marrow. Previous studies showed that reduced radiation dose to the pelvic bone marrow resulted in significant fewer hematologic AEs, which corresponds to the reduced grade ≥2 hematologic AEs with IMRT observed during follow-up in our study. Reduced hematologic AEs may lead to improved clinical outcomes by increasing tolerance for chemotherapy.[8, 20-22]

Limitations of the current study include it being a subanalysis of the PORTEC-3 trial that was not powered to detect a significant difference between the radiation therapy techniques. The relatively small number of patients who received IMRT and the lack of data on dosimetric parameters

and dose-volume histograms, which could have contributed to a better understanding of the reduced physician-reported AEs after IMRT, are further limitations. In addition, IMRT was still in its early phases during the accrual period, with ongoing introduction in many centers. Current standardized protocols with image guided radiation therapy, enabling smaller margins, and increased use of VMAT may result in even more normal tissue sparing and reduction of toxicities. Another limitation was the fact that toxicity and QoL data at 5 years were only available for approximately 60% of patients, and 5-year results should be interpreted with caution. Strengths of this study were the prospective data collection, including data on patient-reported QoL, the extensive follow-up period, and uniform radiation therapy treatment as described by the trial protocol.

For future perspectives, further reduction of morbidity can be expected by ongoing development and implementation of new radiation techniques. Imaging modalities with improved quality for image guided radiation therapy, such as magnetic resonance–guided radiation therapy and 4-dimensional cone-beam computed tomography, and automated treatment planning software provide the opportunity to further reduce unnecessary dose to OARs via smaller margins and daily adaptation to the target volume anatomy. These developments can lead to decreased treatment margins, increased precision, and decreased radiated OAR volume and thus reduced treatment-related AEs and patient-reported symptoms. Moreover, other radiation therapy modalities, such as proton beam radiation therapy, may further reduce dose to OARs, including bowel and bone marrow, even more, and the first studies are being initiated.[23-26] With these developments, the future of radiation therapy holds fewer AEs and increased QoL by more precise and image guided therapy with improvement of clinical outcomes.

CONCLUSIONS

Within the PORTEC-3 trial, IMRT resulted in fewer grade ≥3 AEs during treatment and significantly lower rates of grade ≥2 AEs, specifically diarrhea and hematologic AEs, during follow-up as compared to 3D-conformal radiation therapy. Trends toward fewer patient-reported bowel symptoms were observed after IMRT. Intensity-modulated techniques such as IMRT or VMAT should be the standard techniques for women receiving adjuvant radiation therapy for high-risk EC.

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REFERENCES

1. Heron, D.E., et al., *Conventional 3D conformal versus intensity-modulated radiotherapy for the adjuvant treatment of gynecologic malignancies: a comparative dosimetric study of dose–volume histograms☆.* Gynecologic Oncology, 2003. **91**(1): p. 39-45.
2. Ahamad, A., et al., *Intensity-modulated radiation therapy after hysterectomy: comparison with conventional treatment and sensitivity of the normal-tissue-sparing effect to margin size.* Int J Radiat Oncol Biol Phys, 2005. **62**(4): p. 1117-24.
3. Chan, P., et al., *Dosimetric comparison of intensity-modulated, conformal, and four- field pelvic radiotherapy boost plans for gynecologic cancer: a retrospective planning study.* Radiat Oncol, 2006. **1**: p. 13.
4. Ferrigno, R., et al., *Comparison of conformal and intensity modulated radiation therapy techniques for treatment of pelvic tumors. Analysis of acute toxicity.* Radiat Oncol, 2010. **5**: p. 117.
5. Gandhi, A.K., et al., *Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study.* Int J Radiat Oncol Biol Phys, 2013. **87**(3): p. 542-8.
6. Chen, L.A., et al., *Toxicity and cost-effectiveness analysis of intensity modulated radiation therapy versus 3-dimensional conformal radiation therapy for postoperative treatment of gynecologic cancers.* Gynecol Oncol, 2015. **136**(3): p. 521- 8.
7. Roeske, J.C., et al., *Intensity-Modulated Whole Pelvic Radiation Therapy in Patients with Gynecologic Malignancies.* Int J Radiat Oncol Biol Phys, 2000. **48**(5): p. 1613- 1621.
8. Brixey, C.J., et al., *Impact of Intensity-Modulated Radiotherapy on Acute Hematologic Toxicity in Women with Gynecologic Malignancies.* Int J Radiat Oncol Biol Phys, 2002. **54**(5): p. 1388-1396.
9. Mundt, A.J., et al., *Intensity-Modulated Whole Pelvic Radiotherapy in Women with Gynecologic Malignancies.* Int J Radiat Oncol Biol Phys, 2002. **52**(5): p. 1330-1337.
10. Mundt, A.J., L.K. Mell, and J.C. Roeske, *Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy.* International Journal of Radiation Oncology*Biology*Physics, 2003. **56**(5): p. 1354-1360.
11. Klopp, A.H., et al., *Patient-Reported Toxicity During Pelvic Intensity-Modulated Radiation Therapy: NRG Oncology-RTOG 1203.* J Clin Oncol, 2018. **36**(24): p. 2538-2544.
12. Yeung, A.R., et al., *Improvement in Patient-Reported Outcomes With Intensity- Modulated Radiotherapy (RT) Compared With Standard RT: A Report From the NRG Oncology RTOG 1203 Study.* Journal of Clinical Oncology, 2020. **38**(15): p. 1685-1692.
13. de Boer, S.M., et al., *Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial.* The Lancet Oncology, 2018. **19**(3): p. 295-309.
14. de Boer, S.M., et al., *Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial.* The Lancet Oncology, 2019. **20**(9): p. 1273-1285.
15. Post, C.C.B., et al., *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.* Int J Radiat Oncol Biol Phys, 2020.
16. de Boer, S.M., et al., *Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial.* Lancet Oncol, 2016. **17**(8): p. 1114-26.

17. Jameson, M.G., et al., *Results of the Australasian (Trans-Tasman Oncology Group) radiotherapy benchmarking exercise in preparation for participation in the PORTEC-3 trial.* J Med Imaging Radiat Oncol, 2016. **60**(4): p. 554-9.
18. Fayers, P., *The EORTC QLQ-C30 Scoring Manual (3rd Edition)*. 2001, Brussels: European Organisation for Research and Treatment of Cancer.
19. Ta, M.H., et al., *Comparison of 3D conformal radiation therapy and intensity- modulated radiation therapy in patients with endometrial cancer: efficacy, safety and prognostic analysis.* Acta Oncol, 2019. **58**(8): p. 1127-1134.
20. Klopp, A.H., et al., *Hematologic toxicity in RTOG 0418: a phase 2 study of postoperative IMRT for gynecologic cancer.* Int J Radiat Oncol Biol Phys, 2013. **86**(1): p. 83-90.
21. Mell, L.K., et al., *Bone Marrow-sparing Intensity Modulated Radiation Therapy With Concurrent Cisplatin For Stage IB-IVA Cervical Cancer: An International Multicenter Phase II Clinical Trial (INTERTECC-2).* Int J Radiat Oncol Biol Phys, 2017. **97**(3): p. 536- 545.
22. Huang, J., et al., *Pelvic bone marrow sparing intensity modulated radiotherapy reduces the incidence of the hematologic toxicity of patients with cervical cancer receiving concurrent chemoradiotherapy: a single-center prospective randomized controlled trial.* Radiat Oncol, 2020. **15**(1): p. 180.
23. van de Sande, M.A., et al., *Which cervical and endometrial cancer patients will benefit most from intensity-modulated proton therapy?* Radiother Oncol, 2016. **120**(3): p. 397-403.
24. Dinges, E., et al., *Bone marrow sparing in intensity modulated proton therapy for cervical cancer: Efficacy and robustness under range and setup uncertainties.* Radiother Oncol, 2015. **115**(3): p. 373-8.
25. Arians, N., et al., *Prospective phase-II-study evaluating postoperative radiotherapy of cervical and endometrial cancer patients using protons - the APROVE-trial.* Radiat Oncol, 2017. **12**(1): p. 188.
26. Gort, E.M., et al., *Inter-fraction motion robustness and organ sparing potential of proton therapy for cervical cancer.* Radiother Oncol, 2021. **154**: p. 194-200.

SUPPLEMENTARY DATA

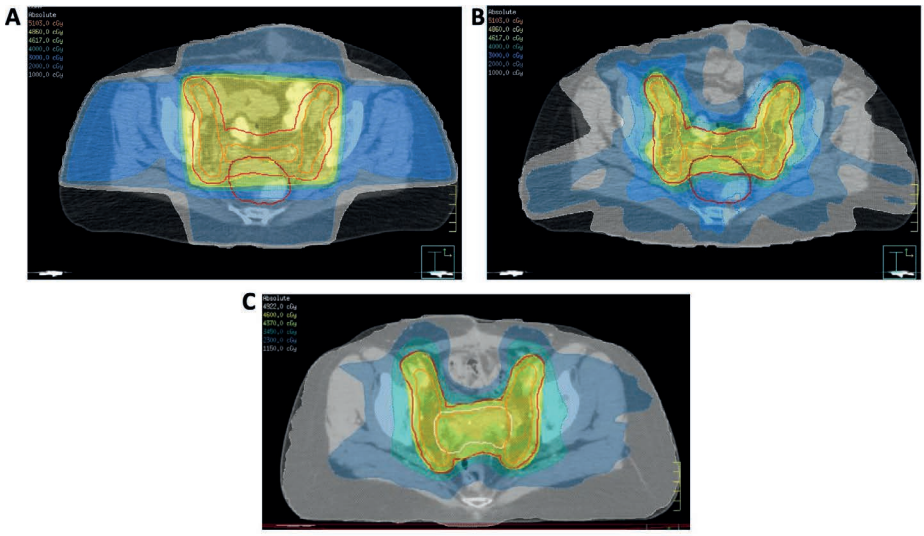
Table E1. Physician-reported toxicity during treatment and the follow-up period.

	During treatment						During follow-up					
	Grade 2		p*	Grade 3-4		p	Grade 2		p*	Grade 3-4		p
	IMRT (n=99)	3DCRT (n=559)		IMRT (n=99)	3DCRT (n=559)		IMRT (n=99)	3DCRT (n=599)		IMRT (n=99)	3DCRT (n=599)	
Any	41 (41%)	172 (31%)	0.91	26 (26%)	211 (38%)	0.03	46 (46%)	267 (48%)	0.01	21 (21%)	176 (31%)	0.04
Any grade 3	-	-		19 (19%)	168 (30%)					20 (20%)	151 (27%)	
Any grade 4	-	-		7 (7%)	43 (8%)					1 (1%)	25 (4%)	
Gastro-intestinal, any	38 (38%)	185 (33%)	1.00	5 (5%)	59 (11%)	0.09	18 (18%)	110 (20%)	0.27	4 (4%)	40 (7%)	0.38
- Diarrhea	29 (29%)	141 (25%)	0.91	3 (3%)	45 (8%)	0.09	4 (4%)	66 (12%)	<0.01	0 (0%)	12 (2%)	0.23
- Nausea	14 (14%)	78 (14%)	1.00	1 (1%)	10 (2%)	1.00	3 (3%)	21 (4%)	0.81	1 (1%)	8 (1%)	1.00
- Vomiting	5 (5%)	35 (6%)	0.83	1 (1%)	4 (1%)	0.56	1 (1%)	21 (4%)	0.10	0 (0%)	4 (1%)	1.00
- Constipation	3 (3%)	35 (6%)	0.25	0 (0%)	1 (<1%)	1.00	6 (6%)	33 (6%)	1.00	1 (1%)	6 (1%)	1.00
- Ileus/obstruction	2 (2%)	6 (1%)	0.40	1 (1%)	3 (1%)	0.48	4 (4%)	9 (2%)	0.34	2 (2%)	23 (4%)	0.41
Genitourinary												
- Dysuria	8 (8%)	24 (4%)	1.00	1 (1%)	0 (0%)	0.15	3 (3%)	16 (3%)	1.00	0 (0%)	1 (0%)	1.00
- Urinary frequency/urgency	5 (5%)	29 (5%)	0.82	0 (0%)	4 (1%)	1.00	8 (8%)	60 (11%)	0.40	1 (1%)	4 (1%)	1.00
- Incontinence	2 (2%)	15 (3%)	1.00	0 (0%)	1 (<1%)	1.00	7 (7%)	65 (12%)	0.19	0 (0%)	9 (2%)	0.37
Pain, any	19 (19%)	104 (19%)	1.00	5 (5%)	30 (5%)	1.00	28 (28%)	140 (25%)	0.73	2 (2%)	38 (7%)	0.07
- Muscle pain	8 (8%)	45 (8%)	1.00	1 (1%)	8 (1%)	1.00	0 (0%)	24 (4%)	0.02	0 (0%)	3 (1%)	1.00
- Arthralgia	7 (7%)	46 (8%)	0.71	1 (1%)	9 (2%)	1.00	5 (5%)	53 (9%)	0.27	1 (1%)	3 (1%)	0.48
- Back/pelvic/limbs	4 (4%)	10 (2%)	0.57	1 (1%)	10 (2%)	1.00	9 (9%)	50 (9%)	1.00	1 (1%)	9 (2%)	1.00
- Abdomen/cramps	5 (5%)	18 (3%)	0.61	1 (1%)	7 (1%)	1.00	8 (8%)	32 (6%)	1.00	0 (0%)	15 (3%)	0.14
- Musculoskeletal	1 (1%)	3 (1%)	1.00	0 (0%)	2 (<1%)	1.00	0 (0%)	16 (3%)	0.56	2 (2%)	4 (1%)	0.22
Fatigue	16 (16%)	59 (11%)	0.33	0 (0%)	10 (2%)	0.37	6 (6%)	23 (4%)	0.33	1 (1%)	4 (1%)	0.56
Neuropathy, any	12 (12%)	70 (13%)	0.46	1 (1%)	22 (4%)	0.23	9 (9%)	72 (13%)	0.76	5 (5%)	14 (3%)	0.19
- Motor	0 (0%)	14 (3%)	0.09	0 (0%)	4 (1%)	1.00	4 (4%)	16 (3%)	0.60	1 (1%)	6 (1%)	1.00
- Sensory	12 (12%)	66 (12%)	0.65	1 (1%)	21 (4%)	0.23	8 (8%)	68 (12%)	0.64	4 (4%)	12 (2%)	0.28
Hematological, any	16 (16%)	103 (18%)	0.23	21 (21%)	145 (26%)	0.38	6 (6%)	101 (18%)	<0.01	7 (7%)	42 (8%)	1.00
Lymphatics (edema)	1 (1%)	10 (2%)	0.70	0 (0%)	2 (<1%)	1.00	6 (6%)	25 (4%)	0.35	1 (1%)	5 (1%)	1.00
Hypertension	4 (4%)	27 (5%)	0.49	0 (0%)	9 (2%)	0.37	8 (8%)	56 (10%)	0.19	0 (0%)	3 (1%)	0.09

*The maximum grade per patient per adverse event is shown; *p-values show significance for grade 2-4 adverse events.*

RT: radiotherapy; 3DCRT: 3D conformal radiotherapy.

Figure E1. Dose distribution of 3D-conformal radiotherapy versus intensity-modulated radiotherapy.



***A.** Four field box technique; **B.** Seven field intensity modulated radiotherapy; **C.** Volumetric arc radiotherapy.*

Figure E2. Percentage of patients who reported "quite a bit" or "very much" of urinary frequency, lower back pain or muscle/joint pain in the total PORTEC-3 cohort, during and after radiotherapy only and after chemoradiotherapy.