3

Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial

R. A. Nout
V. T. H. B. M. Smit
H. Putter
I. M. Jürgenliemk-Schulz
J. J. Jobsen
L. C. Lutgens
E. M. van der Steen-Banasik
J. W. M. Mens
A. Slot
M. C. Stenfert Kroese
B. N. van Bunningen
A. C. Ansink
W. L. van Putten

Lancet. 2010;375(9717):816-823.

Summary

Background: After surgery for intermediate-risk endometrial carcinoma (EC), the vagina is the most frequent site of recurrence. This study established whether vaginal brachytherapy (VBT) is as effective as pelvic external beam radiotherapy (EBRT) in prevention of vaginal recurrence, with fewer adverse effects and improved quality of life.

Methods: In this open-label, non-inferiority, randomised trial undertaken in 19 Dutch radiation oncology centres, 427 patients with stage I or IIA endometrial cancer with features of high-intermediate risk were randomly assigned by a computer-generated, biased coin minimisation procedure to pelvic EBRT (46 Gy in 23 fractions; n=214) or VBT (21 Gy high-dose rate in 3 fractions, or 30 Gy low-dose rate; n=213). All investigators were masked to the assignment of treatment group. The primary endpoint was vaginal recurrence. The predefined non-inferiority margin was an absolute difference of 6% in vaginal recurrence. Analysis was by intention to treat, with competing risk method. The study is registered, number ISRCTN16228756.

Findings: At median follow-up of 45 months (range 18-78), three vaginal recurrences had been diagnosed after VBT and four after EBRT. Estimated 5-year rates of vaginal recurrence were 1.8% (95% CI 0.6 - 5.9) for VBT and 1.6% (0.5 – 4.9) for EBRT (hazard ratio [HR] 0.78, 95% CI 0.17 – 3.49; p=0.74). Five-year rates of locoregional relapse (vaginal or pelvic recurrence, or both) were 5.1% (2.8 – 9.6) for VBT and 2.1% (0.8 – 5.8) for EBRT (HR2.08, 0.71 – 6.09; p=0.17). 1.5% (0.5 – 4.5) vs 0.5% (0.1 – 3.4) of patients presented with isolated pelvic recurrence (HR 3.10, 0.32 – 29.9; p=0.30), and rates of distant metastasis were similar (8.3% [5.1 – 13.4] vs 5.7% [3.3 – 9.9]; HR 1.32, 0.63 – 2.74; p=0.46). We recorded no differences in overall (84.8% [95% CI 79.3 – 90.3] vs 79.6% [71.2 – 88.0]; HR 1.17, 0.69 – 1.98; p=0.57) or disease-free survival (82.7% [76.9 – 88.6] vs 78.1% [69.7 – 86.5]; HR 1.09, 0.66 – 1.78; p=0.74). Rates of acute grade 1-2 gastrointestinal toxicity were significantly lower in the VBT group than in the EBRT group at completion of radiotherapy (12.6% [27/215] vs 53.8% [112/208]).

Interpretation: VBT is effective in ensuring vaginal control, with fewer gastrointestinal toxic effects than with EBRT. VBT should be the adjuvant treatment of choice for patients with endometrial carcinoma of high-intermediate risk.

Introduction

Endometrial carcinoma is the most common gynaecological malignant disease in postmenopausal women in developed countries.[1] About 80% of patients present with early stage disease (International Federation of Gynecology and Obstetrics [FIGO] stage I, limited to the uterine corpus) and have a favourable prognosis. Surgery consisting of total abdominal hysterectomy and bilateral salpingo-oophorectomy is the basis of treatment.

Both the first Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC-1) trial and the Gynecological Oncology Group (GOG) 99 trial compared pelvic external beam radiotherapy (EBRT) with no additional treatment for patients with stage I endometrial carcinoma, and showed that EBRT significantly reduced the rate of locoregional (vaginal or pelvic, or both) recurrence.[2-4] Both trials defined a so-called group of high-intermediate risk that showed the largest absolute reduction of locoregional recurrence after EBRT. In PORTEC-1, major risk factors for recurrence were invasion in the outer half of the myometrium, grade 3 histology, and age greater than 60 years.[2, 4] For patients at high-intermediate risk with two of these three major risk factors, locoregional at 5 years was reduced from 23% to 5% after EBRT.[2, 4] In GOG 99, EBRT provided a 58% hazard reduction of 4-year cumulative recurrence in the group at high-intermediate risk (from 27% to 13%), and reduction of isolated initial local recurrence from 13% to 5%.[3] In both trials this reduction was mainly caused by reduction of vaginal recurrence, which accounted for 75% of locoregional recurrence in the group receiving no additional treatment. EBRT did not improve overall survival, and rates of distant metastases were similar. In PORTEC-1, adverse effects were recorded in 26% of patients receiving EBRT, predominantly mild gastrointestinal toxic effects.[5]

Retrospective studies reported vaginal brachytherapy (VBT) to be very effective in prevention of vaginal recurrence.[6-10] The randomised PORTEC-2 trial was started to investigate whether VBT would be equally effective as EBRT in reduction of vaginal recurrence, with fewer treatment-related toxic effects and improved quality of life. Analysis of quality of life reported by patients in PORTEC-2 during the first two years after treatment has shown that

those who had received EBRT reported significantly more, clinically relevant gastrointestinal symptoms, especially diarrhoea,[11] resulting in restriction of daily activities and decreased social functioning.

This study aimed to compare outcomes and adverse effects after VBT and EBRT, and to establish optimum adjuvant treatment for patients with endometrial carcinoma of high-intermediate risk.

Methods

Patient selection and eligibility criteria

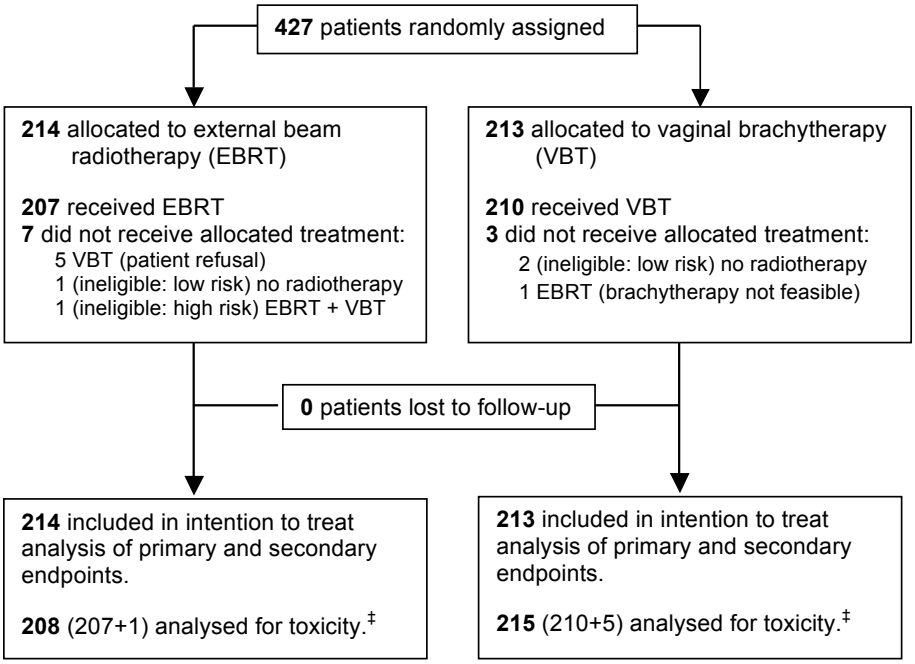
The PORTEC-2 trial was a multicenter randomised trial, in which 19 of the 21 Dutch radiation oncology centres participated. The study was undertaken between May 27, 2002 and Sept 25, 2006. Patients were assessed and operated on by their regional gynaecologist. Initial assessment included pelvic examination, and endometrial tissue biopsy. Preoperative evaluation included chest radiography and haematology and chemistry tests. During surgery a peritoneal cytology specimen was obtained and abdominal exploration undertaken. Surgery consisted of total abdominal hysterectomy and bilateral salpingo-oophorectomy; clinically suspicious pelvic or periaortic lymph nodes were removed, but no routine lymphadenectomy was done. Diagnosis, typing and grading of endometrial carcinoma was done by the regional pathologist. FIGO 1988 staging was assigned on the basis of surgical and pathological findings.[12]

Patients with endometrial adenocarcinoma were eligible for the trial on the basis on the following features of high-intermediate risk: (1) Age greater than 60 years and stage 1C grade 1 or 2 disease, or stage 1B grade 3 disease; and (2) stage 2A disease, any age (apart from grade 3 with greater than 50% myometrial invasion). All patients had a WHO-performance score of 0-2. Exclusion criteria were: serous or clear cell carcinoma; staging lymphadenectomy; interval between surgery and radiotherapy more than 8 weeks; history of previous malignant disease; previous radiotherapy, hormonal therapy or chemotherapy; and previous diagnosis of Crohn's disease or ulcerative colitis. We obtained written informed consent from all patients. The protocol was approved by the Dutch Cancer Society and the Ethics Committees of all participating centres.

Randomisation and masking

Participants were assigned to either EBRT or VBT via internet with an application trial on line process (TOP). Patient details and answers about eligibility questions were entered by the data managers of the participating centres, after which treatment was allocated by TOP with a biased coin minimisation procedure, with stratification factors FIGO stage, radiotherapy centre, brachytherapy (low-dose vs. high-dose rate), and patient age (<60 years vs. ≥60 years). The outcome of the allocation was computer generated and not predictable by the investigators. Once the trial group was assigned, the treatment and the assessment of the outcomes were unmasked.

Figure 1. Trial profile
EBRT= external beam radiotherapy. VBT= vaginal brachytherapy. ‡ Toxicity analysis was performed for treatment received. We did not record data for the total number of patients diagnosed and who received primary treatment in the participating centres.



Procedures

The primary endpoint was vaginal recurrence. Secondary endpoints were locoregional recurrence (vagina or pelvic, or both), distant metastases, overall and disease-free survival, treatment-related toxic effects, and quality of life (reported elswhere11).

The clinical target volume for EBRT consisted of the proximal half of the vagina, the parametrial tissues, the internal and proximal external iliac lymph node region, and the caudal part of the common iliac lymph node chain (up to 1 cm below the level of the promontory). The planning target volume consisted of the clinical target volume with a 1 cm three-dimensional margin.

A dose of 46 Gy, with 2 Gy fractions, five times per week, was prescribed to the planning target volume and specified at the isocenter, with homogeneity requirements according to recommendations of the International Commission of Radiation Units and Measurements (ICRU-50). For all patients computerized treatment planning was done using three-dimensional conformal or multiple field techniques, with individual shielding in all fields. Centres had to complete a dummy-run procedure prior to activation the trial.

Brachytherapy was delivered with a vaginal cylinder, with the reference isodose covering the proximal half of the vagina. The dose was specified at 5 mm distance from the surface of the cylinder. The dose at 5 mm cranially from the vaginal vault along the axis of the cylinder could not vary more than plus or minus 10% of the specified dose. Dose schedules with a low-dose and high-dose rate were prescribed, with a dose equivalent to 45-50 Gy to the vaginal mucosa: 21 Gy in three fractions of 7 Gy, 1 week apart for the high-dose rate; 30 Gy at 50-70 cGy/hr for the low-dose rate; and 28 Gy at 100 cGy/hr in one session for the medium-dose rate. Centres had to use the same treatment schedule throughout the trial. Doses in the bladder and rectum reference points (according to ICRU-38 criteria) and at the vaginal mucosal surface were documented.

Patients were assessed by their radiation oncologist 2-4 weeks after completion of radiotherapy. Alternating follow-up visits to the gynaecologist and radiation oncologist were planned every 3 months in the first 2 years, every 6 months until year 5, and then every year, up to ten years. Pelvic examination was

Table 1. Patient and tumour characteristics.

	EBRT (N=214)		**VBT** (N=213)	
	No. of patients	%	No. of patients	%
Median age ± SD, yrs	69 ± 7		70 ± 7	
Age				
≤ 60 years	8	3.7	8	3.8
60-70 years	109	50.9	99	46.5
> 70 years	97	45.3	106	49.8
KPS				
0	157	73.4	141	66.5
1	56	26.2	66	31.1
2	1	0.5	5	2.4
Co-morbidity				
IBD	4	1.9	2	0.9
Diabetes	28	13.1	34	16.0
Hypertension	75	35.0	75	35.2
Cardiovascular	47	22.0	51	24.0
Other	33	15.4	33	15.5
FIGO stage				
IB	19	8.9	16	7.5
IC	172	80.4	171	80.3
IIA	23	10.7	26	12.2
Grade				
1	99	46.3	103	48.4
2	97	45.3	94	44.1
3	18	8.4	16	7.5
LVSI				
Present	25	11.7	21	9.9
Absent	189	88.3	191	90.1
Distance to serosa				
0-1 mm.	17	14.2	23	16.9
2-3 mm.	46	38.3	43	31.6
4-5 mm.	35	29.2	36	26.5
≥ 6 mm.	22	18.3	34	25
not recorded	94	43.9	77	36.2
median mm. (± SD))	3.8 (±2.5)		4.3 (±3.2)	
Interval surgery-radiotherapy, days (SE)	43.4 (0.8)		42.5 (0.8)	
Duration of radiotherapy, days (SE)	30.9 (0.2)		12.9 (0.4)	
Mean dose, SE (Gy)				
EBRT	46.0 (0.9)			
VBT: HDR‡			21.1 (0.1)	
VBT: MDR‡			28.5 (0.5)	
VBT: LDR‡			29.0 (0.3)	
VBT median cylinder diameter (mm. + range)			30 (20-40)	
VBT mean length of 100% isodose (mm. + SE)			46.5 (0.7)	

EBRT: external beam radiotherapy; VBT: vaginal brachytherapy KPS: Karnofsky Performance Score; IBD: irritable bowel syndrome, LVSI: lymph vascular space invasion
‡VBT was delivered with high-dose-rate (HDR) in 182 (85.4%)patients; with low-dose-rate (LDR) in 19 (9.0%) patients; and medium-dose-rate (MDR) in 8 (3.8%) patients.

Table 2. Recurrence and survival (all patients), after a median follow-up of 45 months.

	Events/Total	Estimated 5-year % (95% CI)	Hazard Ratio (95% CI)*	Log-rank *p* value*
Vaginal Recurrence				
EBRT	4/214	1.6 (0.5 - 4.9)	1	0.74
VBT	3/213	1.8 (0.6 - 5.9)	0.78 (0.17-3.49)	
Pelvic Recurrence				
EBRT	1/214	0.5 (0.1 - 3.4)	1	0.02
VBT	8/213	3.8 (1.9 - 7.5)	8.29 (1.04-66.4)	
Locoregional Recurrence				
EBRT	5/214	2.1 (0.8 - 5.8)	1	0.17
VBT	10/213	5.1 (2.8 - 9.6)	2.08 (0.71-6.09)	
Distant Metastases				
EBRT	13/214	5.7 (3.3 - 9.9)	1	0.46
VBT	16/213	8.3 (5.1 - 13.4)	1.32 (0.63-2.74)	
First Failure Type				
Vaginal Recurrence				
EBRT	2/214	1.1 (0.3 - 4.4)	1	0.57
VBT	1/213	0.9 (0.1 - 6.2)	0.51 (0.05-5.58)	
Pelvic Recurrence				
EBRT	1/214	0.5 (0.1 - 3.4)	1	0.30
VBT	3/213	1.5 (0.5 - 4.5)	3.10 (0.32-29.9)	
Disease Free Survival				
EBRT	31/214	78.1 (69.7 - 86.5)	1	0.74
VBT	32/213	82.7 (76.9 - 88.6)	1.09 (0.66-1.78)	
Overall Survival				
EBRT	26/214	79.6 (71.2 - 88.0)	1	0.57
VBT	29/213	84.8 (79.3 - 90.3)	1.17 (0.69-1.98)	

done at every visit. We assessed acute and late side-effects with the grading system of the European Organisation of Research and Treatment of Cancer and Radiation Therapy Oncology Group (EORTC-RTOG) for radiation toxic effects.14 For assessment of late effects in the vaginal mucosa that were clinically recorded at pelvic examination, EORTC-RTOG grading for mucous membrane was used. Any atrophic changes were reported as grade 1 (minor atrophy), and moderate atrophy with or without telangiectasia as grade 2 mucosal toxic effects. Chest radiograph, blood count and chemistry tests were obtained every year. Vaginal or pelvic recurrences had to be confirmed by histology, and patients with recurrence were screened for distant metastasis.
Eligibility check and randomization were done based on the original pathology diagnosis. Central review of the pathology was done to assess histological type, stage and grade, especially as previous studies have indicated poor reproducibility of tumour grading.4, 15 At review criteria for high-intermediate risk could be confirmed, or patients could be either reclassified to high-risk (non-endometrioid type carcinoma, IC grade 3, or stage IIB or higher), or low-risk groups.

Statistical Analysis

On the basis of data from the PORTEC-1 trial, vaginal recurrence was expected to be 2% after 3 years in the EBRT group. In view of the absence of survival benefit with either EBRT and VBT and of the expected reduced risk of side effects with VBT, the aim of the trial was to estimate the difference in vaginal recurrence with sufficient precision (SE <2%) and to exclude a clinically relevant absolute difference in efficacy. An accrual of 400 patients in 4 years would provide the study with adequate power (85%) to detect a clinically relevant absolute difference of 6% in vaginal recurrence (2% vs 8%, hazard ratio [HR] 4.1) between both arms (one-sided test).

Analysis was done by intention-to-treat. Time-to-event analyses were done with log-rank tests and Cox proportional hazards regression models with date of randomization as starting point. Both log-rank tests and Cox regression models were stratified for FIGO stage, but were essentially the same with and without adjustment. Data on patients who were alive and free of recurrence were censored at date of last follow-up. The competing risks method (with death as competing risk) was used for analysis of the rates of vaginal recurrence, pelvic recurrence, locoregional recurrence and distant metastases.[13] The Kaplan-Meier method was used for overall and disease-free survival. A first failure competing risks analysis was done when the first failure type was distant if there was distant metastasis, with or without simultaneous vaginal or pelvic recurrence. The failure type was pelvic recurrence if there was pelvic recurrence with or without vaginal recurrence; the failure type was vaginal recurrence in the case of isolated vaginal recurrence. Analysis of toxicity was based on treatment received.

All statistical analyses were done with SPSS, version 16.0 (SPSS, Inc, Chicago, IL). Patient- and tumour characteristics and data for toxic effects were compared with chi-square statistics or Fisher's exact test for categorical variables, and *t* test for continuous variables (p-value < 0.05 was considered significant). The study is registered, number ISRCTN16228756.

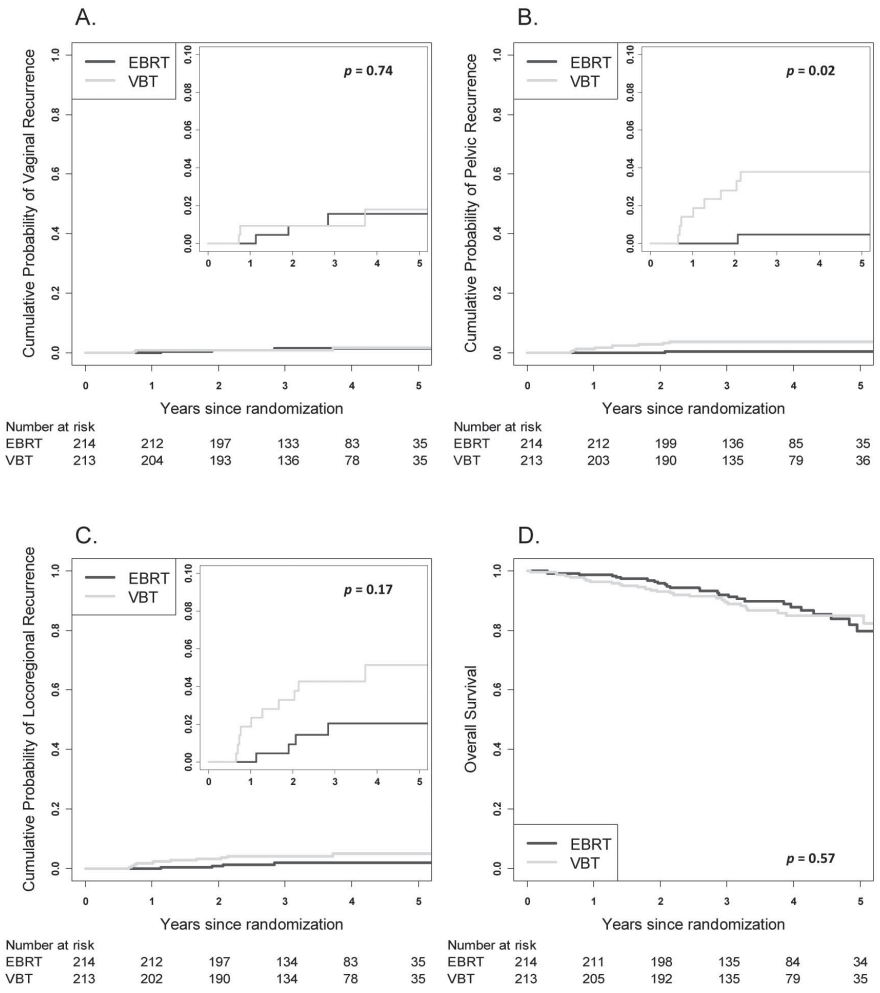


Figure 2. Cumulative probability of vaginal recurrence (A), pelvic recurrence (B), locoregional recurrence (C), and Kaplan-Meier survival curve for overall survival (D). Inserts show curves with adjusted axis from 0 to 10%. EBRT= external beam radiotherapy. VBT= vaginal brachytherapy.

Role of funding source:

The sponsor of the study reviewed and approved the design of the trial and funded data management. The sponsor had no role in data collection, data interpretation, data analysis, or writing of the report. The central data manager, principal and associate investigators, and trial statistician had full

access to the data. The decision to submit for publication was made after presentation and discussion with the trial management group (co-investigators, trial statisticians, trial coordinator, and trial pathologist).

Table 3. Recurrence and survival for true-HIR patients after pathology review (N=366).

	Events/Total	Estimated 5-year % (95% CI)	Hazard Ratio (95% CI)*	Log-rank *p* value*
Vaginal Recurrence				
EBRT	4/183	1.9 (0.6 - 5.8)	1	0.39
VBT	2/183	1.5 (0.4 - 6.5)	0.48 (0.09-2.64)	
Pelvic Recurrence				
EBRT	1/183	0.6 (0.1 - 4.0)	1	0.06
VBT	6/183	3.3 (1.5 - 7.3)	6.10 (0.73-50.7)	
Locoregional Recurrence				
EBRT	5/183	2.4 (0.9 - 6.5)	1	0.42
VBT	8/183	4.8 (2.4 - 9.7)	1.58 (0.52-4.86)	
Distant Metastases				
EBRT	10/183	5.0 (2.6 - 9.4)	1	0.79
VBT	11/183	6.4 (3.6 - 11.5)	1.12 (0.48-2.64)	
Disease Free Survival				
EBRT	24/183	80.2 (71.4 - 89.0)	1	0.89
VBT	25/183	84.5 (78.6 - 90.4)	1.04 (0.59-1.82)	
Overall Survival				
EBRT	19/183	82.1 (73.5 - 90.7)	1	0.66
VBT	22/183	86.2 (80.5 - 91.9)	1.15 (0.62-2.13)	

EBRT: external beam radiotherapy, VBT: vaginal brachytherapy
**Both log-rank tests and Cox proportional hazards models are stratified for FIGO stage.*

Results

Figure 1 shows the trial profile. 427 patients were randomly allocated to EBRT (n=214) or VBT (n=213). Data were frozen for analysis on 19 May 2009 and all patients were entered in the intention-to-treat analysis. Patient and tumour characteristics were well balanced between the groups (table 1). Table 2 shows radiotherapy details.

23 (5%) protocol violations occurred, of which 12 (3%) were major (seven in EBRT group, five in VBT group). Eleven patients did not receive the allocated treatment, one of whom died of cardiac arrest before the start of the first treatment (figure 1). Two patients received a higher brachytherapy dose (11 Gy and 10 Gy per session), because of inaccuracies while introducing a new treatment planning system at that centre.

At median follow-up of 45 months (range 18-78 months), four vaginal recurrences had been diagnosed after EBRT and three after VBT. Estimated 5-year vaginal recurrence rates were 1.8% (95% CI 0.6 – 5.9%) after VBT and 1.6% (95% CI 0.5 – 4.9%) after EBRT (log-rank p=0.74; figure 2, table 3). The HR

for vaginal recurrence after VBT compared with EBRT was 0.78 (95% CI 0.17-3.49), indicating that a true hazard ratio of 3.5 is highly unlikely. A true hazard ratio of 3.5 corresponds with an absolute difference of 4.8% (i.e. 2% after EBRT versus 6.8% after VBT), which reliably excludes the clinically relevant difference in vaginal recurrence rate of 6% that the trial aimed to exclude. We recorded no significant difference in 5-year locoregional recurrence, despite a higher rate of pelvic recurrence after VBT (table 3). Moreover, first failure analysis showed that most patients with pelvic recurrence had simultaneous distant metastases (table 3). Five-year rates of distant metastases did not differ significantly between groups (table 3).

55 patients died: 26 after EBRT and 29 after VBT. Of the 26 patients assigned to EBRT who died, 16 (62%) died from intercurrent diseases and ten (38%) from endometrial cancer. Of the 29 patients assigned to VBT who died, 14 (48%) died from intercurrent diseases and 15 (52%) from endometrial cancer. Overall and disease-free survival at 5 years were 84.8% (95% CI 79.3 – 90.3) and 82.7% (76.9 – 88.6), respectively, for VBT and 79.6% (71.2 – 88.0) and 78.1% (69.7 – 86.5), respectively, for EBRT, with overlapping survival curves (Figure 2).

Central pathology review of 367 (86%) of the patients had been completed at the time of analysis (183 [86%] patients in the EBRT group and 184 [86%] in the VBT group). Tumour grading showed poor reproducibility, especially for grade 2 (Kappa 0.34), which is consistent with previous studies. Shifts were mainly detected from grade 2 to grade 1 disease, and to a lesser extent from grade 2 to grade 3 disease (original vs. review grade 1: 48.5% [177/365] vs. 78.6% [287/365]; grade 2: 44.4% [162/365] vs. 9.0% [33/365]; grade 3: 7.1% [26/365] vs. 12.3% [45/365], with similar proportions in EBRT and VBT groups. Central review recorded 12 (3%) cases with non-endometrioid type of carcinoma (six patients in each group).

After central pathology review, 34 (8%) patients had features of high-risk disease (19 [9%] in EBRT group vs. 15 [7%] in VBT group); 27 (6%) were low risk, and therefore in retrospect ineligible (12 [6%] vs. 15 [7%]). Analysis of outcomes of the 366 patients (86%) who remained high-intermediate risk (true high-intermediate risk) at review confirmed the findings of the intention-to-treat analysis (table 4). Per-protocol analysis did not change these results

(data not shown), since there were no recurrences and only one intercurrent death in the VBT group in the six patients who had not received their allocated treatment.

A significantly higher rate of distant metastasis was recorded in patients diagnosed as high risk, or with more advanced stages, or both, after pathology review than in cases with true high-intermediate risk (25.6% [95% CI 9.7 – 41.5] at 5 years, vs. 5.8% [3.3 – 8.3], p<0.0001), with significantly lower overall survival (57.6% [37.4 – 77.8] vs. 84.2% [79.1 – 89.3], p<0.0001) and disease-free survival (54.2% [31.6 – 75.0] vs. 82.4% [77.1 – 87.7], p<0.0003), without differences between the EBRT and VBT groups.

Grade 1 and 2 gastrointestinal (EORTC-RTOG small/large intestine) toxic effects increased significantly at completion of EBRT compared with VBT (EBRT 53.8% [112/208] vs. VBT 12.6% [27/215]). This difference decreased with further follow-up and lost its statistical significance after 24 months (figure 3). For patients assigned to VBT, gastrointestinal toxic effects remained at baseline level (figure 3). Late grade 3 gastrointestinal toxic effects were reported in four (2%) patients receiving EBRT and in one (<1%) receiving VBT, requiring surgery for bowel obstruction due to adhesions or fibrosis. No treatment-related deaths occurred. From 6 months onwards, grade 1 - 2 mucosal atrophy increased, with significantly more grade 2 atrophy after VBT than after EBRT (figure 3). Grade 3 atrophy (marked atrophy with or without shortening or narrowing) was reported in only 1 (<1%) patient receiving EBRT and four (2%) receiving VBT.

Discussion

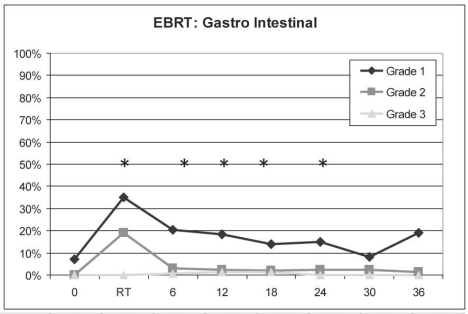
The PORTEC-2 trial compared the efficacy and toxicity of EBRT and VBT for endometrial cancer of high-intermediate risk. At a median follow-up of 45 months, very few vaginal recurrences occurred in both treatment groups, showing VBT to be very effective in ensuring of local control. The vaginal recurrence rate after EBRT is very similar to the rate of 2.2% at 5 years in the first PORTEC trial in patients at intermediate risk, showing consistency of this main finding in both trials.[2]

After PORTEC-1 and GOG#99, the indication for radiotherapy has become restricted to patients with features of high-intermediate risk, and thus most patients with endometrial cancer are treated with surgery alone (with radiotherapy as effective salvage treatment for the occasional patient with relapse). Use of radiotherapy has been justified for patients thought to be at high-intermediate risk, since radiotherapy reduces their 20% risk of locoregional recurrence to 5%, maximising initial local control and relapse-free survival. Even with no survival benefit, radiotherapy spares these patients the psychological stress of recurrence and the morbidity of intensive treatment for relapse. PORTEC-2 shows that patients at high-intermediate risk, about 30% of all patients with endometrial cancer, can be safely treated with vaginal brachytherapy alone, with fewer side-effects and improved quality of life.[11] EBRT will thus be used only for the 15% of patients with high-risk or advanced disease.

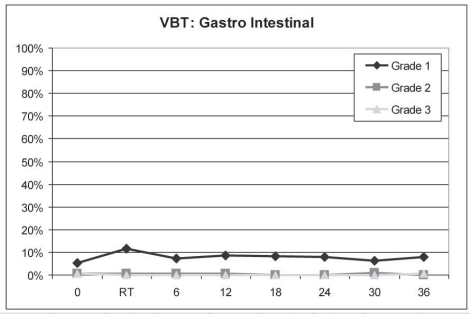
A limitation of the trial design might be that we posed a non-inferiority question, but used a design that aimed to establish the actual difference in vaginal recurrence with sufficient precision, while choosing an absolute non-inferiority margin of 6% - i.e., a power of 85% to exclude a difference in vaginal recurrence rate of 6% at 3 years. This margin of reduced efficacy of VBT was regarded as clinically acceptable in view of the absence of a survival benefit, the expected reduced toxic effects of VBT, and the fact that effective salvage treatment is available in case of vaginal recurrence.

Almost all pelvic recurrences after VBT were part of widespread disease recurrence. The rates of distant metastases were low and similar in both groups. Locoregional recurrence rates in both groups were very similar to those reported in previous randomised trials in patients with intermediate risk, which varied between 2% to 4%.[2, 3, 16, 17]

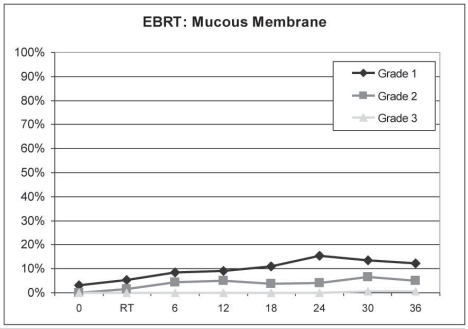
Both GOG#99 and PORTEC-1 trials showed that vaginal recurrences accounted for about 75% of recurrences in the control group.[2, 3] PORTEC-2 has shown that vaginal brachytherapy can be as effectively used for patients at high-intermediate risk to ensure vaginal control. This efficacy of VBT also explains the fairly low rate of isolated vaginal and pelvic recurrence in the control group (6.1% vs. 3.2% for EBRT) of the ASTEC/EN5 trial, the most recently reported randomised trial comparing EBRT with no additional therapy, in which 51% of



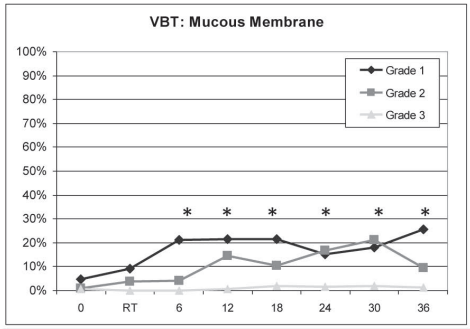
	0	RT	6	12	18	24	30	36
Grade 1	7,1%	34,9%	20,4%	18,5%	14,1%	15,0%	8,0%	19,0%
Grade 2	0,0%	18,9%	3,0%	2,5%	1,9%	2,4%	2,3%	1,2%
Grade 3	0,0%	0,0%	0,6%	1,2%	1,3%	0,0%	0,0%	0,0%



	0	RT	6	12	18	24	30	36
Grade 1	5,2%	11,5%	7,4%	8,7%	8,3%	8,0%	6,2%	8,0%
Grade 2	0,5%	0,5%	0,6%	0,6%	0,0%	0,0%	1,0%	0,0%
Grade 3	0,5%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,5%



	0	RT	6	12	18	24	30	36
Grade 1	3,3%	5,4%	8,5%	9,1%	11,0%	15,3%	13,5%	12,3%
Grade 2	0,0%	1,5%	4,3%	4,9%	3,9%	4,0%	6,7%	4,9%
Grade 3	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,5%	0,5%



	0	RT	6	12	18	24	30	36
Grade 1	4,8%	9,3%	21,1%	21,4%	21,6%	15,3%	17,9%	25,7%
Grade 2	1,0%	3,9%	4,1%	14,5%	10,5%	16,9%	21,1%	9,5%
Grade 3	0,5%	0,0%	0,0%	0,6%	1,9%	1,6%	1,9%	1,4%

*Figure 3. EORTC-RTOG early and late gastro intestinal (small/large intestine) and mucous membrane toxicity at pelvic examination. At every follow-up timepoint the toxicity rate represents the number of patients with toxicity as percentage of the total number of patients that have reached that follow-up time point. There were no grade 4 or 5 toxicities. EBRT= external beam radiotherapy. VBT= vaginal brachytherapy. RT= at completion of radiotherapy. EORTC-RTOG= European Organisation of Research and Treatment of Cancer and Radiation Therapy Oncology Group. *Time points showing significant (p<0.05) difference between EBRT and VBT.*

patients had received vaginal brachytherapy.[17] Moreover, 30% of patients in ASTEC/EN5 and all in GOG#99 underwent a staging lymphadenectomy, whereas the low rates of locoregional recurrence in PORTEC-2 were obtained without routine lymphadenectomy, which accords with the findings of randomised trials showing no survival improvement with lymphadenectomy.[18, 19]

Rates of mild-to-moderate gastrointestinal toxic effects after EBRT in the PORTEC-2 trial were similar to other randomised trials. Gastrointestinal symptoms were most pronounced during and immediately after EBRT and gradually decreased - a pattern very similar to the quality-of-life diarrhoea score. However, effect on daily activities persisted with further follow-up. Patients assigned to VBT reported very few gastrointestinal symptoms.[11]

Assessment of vaginal toxicity is complex, and some grading systems include the impact on sexual functioning (common terminology criteria for adverse events v3.0), whereas others do not (EORTC/RTOG).[14, 20, 21] For PORTEC-2 we decided to record mucosal atrophy and assess the effect of mucosal side-effects on sexual functioning with the quality-of-life sections on sexual activity and vaginal dryness. The vaginal mucosa surface dose is higher with VBT than with EBRT, leading to more grade 2 atrophy. Grade 3 atrophy (substantial atrophy with or without shortening of the vagina) was reported in only five patients (four in VBT group and one in EBRT group). Patient-reported rates of sexual activity increased during the first 6 months after treatment and remained stable thereafter, without significant differences between the treatment groups.[11] Sexual functioning and activity rates (40% at 12 months) were similar to those reported for elderly women in a population-based analysis.[22]

Central pathology review was done because previous work of our group and others had shown discordances in pathological diagnoses, with 8% discrepancies altering patient management.[4, 15] A poor reproducibility of the intermediate grade (grade 2) was confirmed. Additionally, 3% non-endometrioid histological types were diagnosed. On the basis of revised pathologic changes 86% of the patients were true high-intermediate risk, whereas 6% had low-risk and 8% high-risk features. The results of this central pathology review did not change the main outcomes of the study. However, patients shown to be at high risk at review had a significantly higher rate of distant metastasis and lower survival rates, confirming the rationale for trials that include chemotherapy for patients at high risk. In the PORTEC-3 trial, pathology review is mandatory before randomisation, and high-risk patients are randomly assigned between EBRT alone and EBRT with concurrent and adjuvant chemotherapy.

In conclusion, VBT is very effective in ensuring local control, keeping to a minimum the risk of vaginal recurrence, which is the most frequent site of disease recurrence in patients with endometrial carcinoma of high-intermediate risk. VBT achieves excellent vaginal control and rates of locoregional recurrence, overall and disease-free survival that are similar to EBRT, and quality of life and gastrointestinal toxic effects are significantly better with VBT. VBT should be the adjuvant treatment of choice for patients with endometrial carcinoma of high-intermediate risk.

Reference List

1. Bray F, Loos AH, Oostindier M, Weiderpass E. Geographic and temporal variations in cancer of the corpus uteri: incidence and mortality in pre- and postmenopausal women in Europe. Int J Cancer 2005; 117(1):123-131.
2. Creutzberg CL, van Putten WL, Koper PC et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000; 355(9213):1404-1411.
3. Keys HM, Roberts JA, Brunetto VL et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004; 92(3):744-751.
4. Scholten AN, van Putten WL, Beerman H et al. Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys 2005; 63(3):834-838.
5. Creutzberg CL, van Putten WL, Koper PC et al. The morbidity of treatment for patients with Stage I endometrial cancer: results from a randomized trial. Int J Radiat Oncol Biol Phys 2001; 51(5):1246-1255.
6. Alektiar KM, Venkatraman E, Chi DS, Barakat RR. Intravaginal brachytherapy alone for intermediate-risk endometrial cancer. Int J Radiat Oncol Biol Phys 2005; 62(1):111-117.
7. Anderson JM, Stea B, Hallum AV, Rogoff E, Childers J. High-dose-rate postoperative vaginal cuff irradiation alone for stage IB and IC endometrial cancer. Int J Radiat Oncol Biol Phys 2000; 46(2):417-425.
8. Chadha M, Nanavati PJ, Liu P, Fanning J, Jacobs A. Patterns of failure in endometrial carcinoma stage IB grade 3 and IC patients treated with postoperative vaginal vault brachytherapy. Gynecol Oncol 1999; 75(1):103-107.
9. Rittenberg PV, Lotocki RJ, Heywood MS, Krepart GV. Stage II endometrial carcinoma: limiting post-operative radiotherapy to the vaginal vault in node-negative tumors. Gynecol Oncol 2005; 98(3):434-438.
10. Weiss E, Hirnle P, Arnold-Bofinger H, Hess CF, Bamberg M. Adjuvant vaginal high-dose-rate afterloading alone in endometrial carcinoma: patterns of relapse and side effects following low-dose therapy. Gynecol Oncol 1998; 71(1):72-76.
11. Nout RA, Putter H, Jurgenliemk-Schulz IM et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol 2009; 27(21):3547-3556.
12. Shepherd JH. Revised FIGO staging for gynaecological cancer. Br J Obstet Gynaecol 1989; 96(8):889-892.
13. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007; 26(11):2389-2430.

14. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995; 31(5):1341-1346.
15. Scholten AN, Smit VT, Beerman H, van Putten WL, Creutzberg CL. Prognostic significance and interobserver variability of histologic grading systems for endometrial carcinoma. Cancer 2004; 100(4):764-772.
16. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 1980; 56(4):419-427.
17. Blake P, Swart AM, Orton J et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet 2009; 373(9658):137-146.
18. Benedetti PP, Basile S, Maneschi F et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2008; 100(23):1707-1716.
19. Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009; 373(9658):125-136.
20. ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf 2003. Trotti A, Colevas AD, Setser A et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003; 13(3):176-181.
21. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med 2007; 357(8):762-774.