

Long-term Outcome and Late Side Effects in Endometrial Cancer Patients Treated with Surgery and Postoperative Radiation Therapy

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ABSTRACT

Background. We retrospectively reviewed the long-term outcome and late side effects of endometrial cancer (EC) patients treated with different techniques of postoperative radiotherapy (PORT).

Methods. Between 1999 and 2012, 237 patients with EC were treated with PORT. Two-dimensional external beam radiotherapy (2D-EBRT) was used in 69 patients (30 %), three-dimensional EBRT (3D-EBRT) in 51 (21 %), and intensity-modulated RT (IMRT) with helical Tomotherapy in 47 (20 %). All patients received a vaginal brachytherapy (VB) boost. Seventy patients (29 %) received VB alone.

Results. After a median of 68 months (range, 6–154) of follow-up, overall survival was 75 % [95 % confidence interval (CI), 69–81], disease-free survival was 72 % (95 % CI, 66–78), cancer-specific survival was 85 % (95 % CI, 80–89), and locoregional control was 86 % (95 % CI, 81–91). The 5-year estimates of grade 3 or more toxicity and second cancer rates were 0 and 7 % (95 % CI, 1–13) for VB alone, 6 % (95 % CI, 1–11) and 0 % for IMRT + VB, 9 % (95 % CI, 1–17) and 5 % (95 % CI, 1–9) for 3D-EBRT + VB, and 22 % (95 % CI, 12–32) and 12 % (95 % CI, 4–20) for 2D-EBRT + VB ($P = 0.002$ and $P = 0.01$), respectively.

Conclusions. Pelvic EBRT should be tailored to patients with high-risk EC because the severe late toxicity observed might outweigh the benefits. When EBRT is prescribed for

EC, IMRT should be considered, because it was associated with a significant reduction of severe late side effects.

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries.^{1,2} At the time of diagnosis, most patients present with early-stage disease, and low-risk patients have a risk of locoregional recurrence (LRR) of 5–10 %. However, high- to intermediate-risk patients harbor a combination of high-grade, deep myometrial invasion and/or lymphovascular space invasion (LVSI), with a risk of LRR of up to 27 %.³ Randomized studies have shown that postoperative radiotherapy (PORT) decreases the LRR rate without affecting overall survival (OS). However, two-thirds of the patients in those trials had low-risk disease and a substantial risk of dying as a result of competing hazards.^{3–8} The long-term outcome of these trials also confirmed the morbidity risks of adjuvant PORT using mainly two-dimensional (2D) external beam radiotherapy (EBRT) techniques.⁹ The postoperative radiotherapy in EC (PORTEC-2) randomized trial showed that the toxicity of PORT using three-dimensional (3D)-EBRT techniques outweighs the benefits and that vaginal brachytherapy (VB) alone can be enough to avoid local recurrences in the subgroup of patients with high- to intermediate-risk factors (grade 1–2 tumors, >50 % myometrial invasion, endometrioid type, age >60 years, and no LVSI).¹⁰ Pelvic radiotherapy (RT) has changed dramatically over the last few decades with the introduction of intensity-modulated RT (IMRT). The question that remains open is whether IMRT will lead to a reduced rate of severe side effects. Studies have found evidence of an increased risk of secondary neoplasms after PORT, and some investigators have recently postulated that IMRT can potentially increase the risk of second cancers.^{9,11,12} We

aimed in this study to assess a population-based cohort who received adjuvant PORT over a 12-year period with different technique of RT. In our series, IMRT was delivered with helical Tomotherapy (Accuray, Madison, WI). Tomotherapy is a new generation 6-MV photon accelerator that allows helical delivery of highly conformal and homogeneous doses associated with daily image-guided RT. We assessed the severe late toxicity (grade 3 or more) and the incidence of second cancers.

METHODS

Study Population

After approval by the local ethics committee, we retrospectively reviewed the charts of 237 eligible patients from a total of 245 EC patients who received adjuvant PORT between 1999 and 2012 at the Lausanne University Hospital. Inclusion criteria were a pathologic diagnosis of EC, stage I–IVA according to the International Federation of Gynecology and Obstetrics (FIGO) 1988 definition, and a minimum of 6 months of follow-up.¹³ One patient was excluded from the analysis because of disseminated disease, and 7 patients were excluded for incomplete follow-up. Data were obtained from the electronic and written medical records and included age at diagnosis, date of diagnosis, date of surgery, type of surgical procedure, number of pathologically examined lymph nodes, surgical margins, histology, grade, depth of myometrial invasion, stage, LVSI, type and dose of PORT, date and location of recurrence, date of last follow-up, date of death, incidence and types of second cancers, and late side effects (grade 3 or more) based on common terminology criteria for adverse events version 4.0, which were confirmed from follow-up records and surgical and/or procedural interventions. Sites of failure were grouped into isolated vaginal recurrence, LRR (pelvic and/or paraaortic), and distant metastases (extraabdominal sites and positive peritoneal cytology).

Statistical Considerations

Proportions were compared by using the Chi square test for values of 5 or higher and with Fisher's exact test for values of less than 5. Survival curves were estimated by using the Kaplan–Meier method. Time to any event was measured from the day RT started. Death certificates confirmed date of deaths. If clinical or pathologic evidence of active, recurrent disease was present, deaths were attributed to EC. The events were death (all causes) for OS, EC-related mortality for cancer-specific survival (CSS), and death (all causes) or relapse for disease-free survival

(DFS). For the locoregional control (LRC) rate, the event consisted of local or regional relapse. Confidence intervals (CI) were calculated from standard errors. In univariate analyses, differences between groups were assessed by using the log-rank test. All obtained significant *P* values were corrected for multiple comparisons with the Bonferroni correction method in which the *P* values are multiplied by the number of comparisons. In multivariate analyses, we screened for prognostic factors with a *P* value of less than 0.05 in univariate analyses by using the Cox regression analysis to define the independent contribution of each prognostic factor. A *P* value of <0.05 was considered to be statistically significant. All data were examined using JMP version 9.0.1 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

A total of 237 patients with EC were identified with complete follow-up. Patients' surgical, pathologic, and treatment characteristics are detailed in Table 1. The median age was 69 years (range, 37–90 years).

Surgery

All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) including abdominal washing, with (*n* = 126) or without (*n* = 111) lymphadenectomy.

Radiotherapy

RT started 6–8 weeks after surgery and was delivered by using a two-dimensional four-field technique (2D-EBRT) in 69 patients (30 %), four-field conformal RT (3D-EBRT) in 51 (21 %), and Tomotherapy in 47 (20 %). All of the patients treated in the Tomotherapy group had daily image-guided RT using helical megavoltage-based computed tomography. All patients treated with different techniques of EBRT also received a VB boost. Seventy patients (29 %) were treated with postoperative VB alone. Patients treated with 2D-EBRT had the radiation portals determined using a kilovoltage simulator. From the introduction of 3D-EBRT, target volumes and organs at risk were contoured on a computed tomography image, and personalized shielding was applied by using the multileaf collimator. For both 2D-EBRT and 3D-EBRT, the radiation fields extended from the anterior aspect of the pubic symphysis to the L5–S1 interspace and laterally posteriorly up to the middle sacrum. With the introduction of helical Tomotherapy, the radiation volumes were based on the

radiation therapy oncology group consensus guidelines, including the irradiation of common iliac nodes.¹⁴ The median EBRT dose was 45 Gy (range, 41.4–50.4 Gy) in fractions of 1.8 Gy. VB was administered to the upper 3 cm of the vagina by using a high-dose rate technique delivered via vaginal cylinders; the dose was prescribed to the vaginal mucosa (0.5 cm from the cylinder surface). The median number of VB fractions was 3 (range, 2–6), and the median VB dose was 5 Gy per fraction (range, 3–7.5 Gy). The most frequent VB regimen was 10 Gy in 2 fractions for those previously receiving EBRT (VB boost) and 20 Gy in 4 fractions for those only receiving VB.

Disease Outcome

In a median follow-up of 68 months (range, 6–154 months), the 5-year OS was 75 % (95 % CI, 69–81), DFS was 72 % (95 % CI, 66–78), CSS was 85 % (95 % CI, 80–89), and LRC was 86 % (95 % CI, 81–91). By the end of follow-up, 161 of 237 (68 %) patients were alive without disease, and 12 of 237 were alive with recurrent disease. Thirty-three of 237 (14 %) patients died of EC, and 31 of 237 (13 %) died of intercurrent diseases (24 cardiovascular, 6 solid tumors, and 1 treatment-related toxicity). A total of 47 patients (20 %) experienced a recurrence. In univariate analyses, statistically significant factors unfavorably influencing OS and DFS were patient age (>69 years), presence of LVSI, advanced stage, papillary-serous or clear-cell histology, grade 3 tumors, absence of lymphadenectomy, presence of positive lymph nodes, and positive abdominal washing. For CSS and LRC, the previously mentioned parameters applied, except for age (Table 2). After multivariate analyses, the remaining independent prognostic factors unfavorably influencing OS and DFS were age (>69 years), advanced stage, positive LVSI, absence of lymphadenectomy, and grade 3 histology. For CSS and LRC, the previously mentioned variables applied except for age (Table 3).

The 5-year LRC rate was 89 % (95 % CI, 80–96) for patients treated with VB alone versus 85 % (95 % CI, 79–91) for those treated with EBRT + VB ($P = 0.5$). Among those treated with VB alone, there was an increased proportion of patients with endometrioid-type histology [endometrioid type ($n = 62$) versus serous type or clear cell ($n = 8$); $P = 0.0026$], grade 1–2 [grade 1–2 ($n = 67$) versus grade 3 ($n = 3$), $P < 0.0001$], earlier-stage tumors [Ia, b, and IIa ($n = 23$), Ic ($n = 42$), and IIb ($n = 5$); $P < 0.0001$], and absence of LVSI [LVSI absent ($n = 64$), LVSI present ($n = 6$); $P < 0.0001$]. When comparing patients ($n = 60$) who fit the PORTEC-2 inclusion criteria, i.e., stage I tumors, patients >60 years old (Ic and grade 1 or 2), or Ib (grade 3) or stage IIa tumors at any age excluding grade 3 or >50 % myometrial invasion, with

TABLE 1 Patients' surgical, pathologic, and treatment characteristics ($n = 237$)

Characteristic	<i>n</i>	%
1988 FIGO stage		
Ia	5	2
Ib	54	22.7
Ic	75	31.6
IIa	16	6.7
IIb	46	19.4
IIIa	6	2.5
IIIb	2	0.8
IIIc	30	12.6
IVa	1	0.4
LVSI		
Positive	77	32.5
Negative	160	67.5
Grade		
1–2	169	71.3
3	68	28.6
Histology		
Clear cell/serous papillary	56	23.6
Endometrial type	181	76.3
Pelvic lymphadenectomy		
Performed	126	53
Not performed	111	47
Paraortic lymphadenectomy		
Performed	35	14.7
Not performed	202	85.2
Radiotherapy technique		
VB	70	29.5
2D-EBRT + VB	69	29
3D-EBRT + VB	51	21.5
Tomotherapy + VB	47	20

FIGO international federation of gynecology and obstetrics staging system, LVSI lymphovascular space invasion, VB vaginal cuff brachytherapy, 2D-EBRT two-dimensional external beam radiotherapy, 3D-EBRT three-dimensional external beam radiotherapy

those without the PORTEC-2 criteria ($n = 177$), the 5-year LRC was 96 % (95 % CI, 91–100) versus 83 % (95 % CI, 77–89; $P = 0.02$), respectively.¹⁰

Toxicity

By the end of follow-up, 24 patients (9.7 %) developed severe late toxicity (grade 3 or more). Two patients developed urethral stenosis requiring surgery, resulting in permanent urinary incontinence. Three patients developed synchronous urethral stenosis and rectovaginal fistulas. Sixteen patients had intestinal toxicity (bowel stenosis and/or rectovaginal fistulas). One patient died because of small-

TABLE 2 Univariate analysis

Variable	<i>n</i>	5-Year OS (%)	95 % CI	<i>P</i> value	5-Year DFS (%)	95 % CI	<i>P</i> value	5-Year CSS (%)	95 % CI	<i>P</i> value	5-Year LRC (%)	95 % CI	<i>P</i> value
All patients	237	75	69–81		72	66–78		85	80–89		86	81–91	
Age (years)													
<69	116	83	75–91	0.0004	82	75–89	0.0004	87	81–93	0.25	88	82–94	0.49
>69	121	68	59–77	0.003 ^a	62	52–71	0.003 ^a	82	75–89		85	78–92	
LVSI													
Negative	160	82	76–88	0.0004	78	71–85	<0.0001	88	82–93	0.007	90	85–95	0.002
Positive	77	60	46–74	0.003 ^a	54	41–67	0.0008 ^a	77	67–87	0.06 ^a	75	63–87	0.02 ^a
FIGO stage													
Ia/b/IIA	75	86	78–94		82	73–91		94	88–99		94	89–99	
Ic	75	78	67–89	0.0013	75	67–73	0.001	89	81–97	0.0002	93	87–99	0.0001
IIb	46	61	45–77	0.01 ^a	62	47–77	0.008 ^a	71	57–85	0.002 ^a	74	64–84	0.0008 ^a
III	41	54	37–81		58	41–75		63	45–87		60	50–70	
Histology													
Endometrioid	181	77	70–84	0.06	75	68–82	0.01	88	83–93	0.003	89	84–94	0.01
Clear cell/papillary	56	69	55–82		61	48–74	0.08 ^a	73	61–85	0.02 ^a	79	67–91	0.08 ^a
Grade													
1–2	169	80	73–87	0.0006	79	72–85	0.0002	89	84–94	0.004	89	84–94	0.04
3	68	63	50–76	0.005 ^a	51	37–65	0.002 ^a	73	60–86	0.03 ^a	73	58–88	0.32 ^a
Lymphadenectomy													
Not performed	111	69	60–78	0.01	65	57–75	0.03	75	65–82	0.01	76	69–83	0.04
Performed	126	80	72–88	0.08 ^a	78	70–86	0.24 ^a	88	82–94	0.08 ^a	86	80–92	0.32 ^a
Lymph nodes													
Positive	28	57	55–59	0.02	58	56–60	0.005	71	53–89	0.01	65	63–67	0.0001
Negative	209	77	71–83	0.16 ^a	74	68–80	0.04 ^a	86	81–91	0.08 ^a	89	84–93	0.0008 ^a
Washing													
Negative	222	77	71–83	0.03	74	68–80	0.009	86	81–91	0.05	88	83–93	0.0029
Positive	15	51	48–54	0.24 ^a	45	42–48	0.07 ^a	67	64–70	0.4 ^a	65	62–68	0.02 ^a

LVSI lymphovascular space invasion, OS overall survival, DFS disease-free survival, CSS cancer-specific survival, LRC locoregional control, CI confidence interval, FIGO international federation of gynecology and obstetrics staging system

^a *P* values after Bonferroni multiple correction analysis

TABLE 3 Multivariate Cox analysis

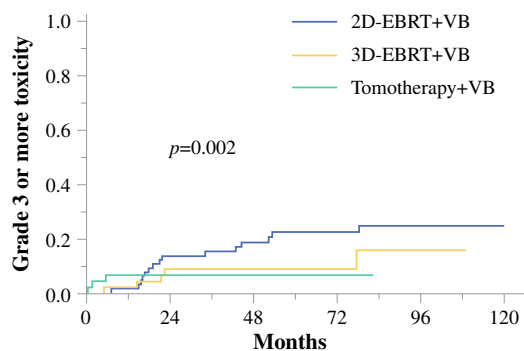
Variable	OS		DFS		CSS		LRC	
	RR	<i>P</i> value	RR	<i>P</i> value	RR	<i>P</i> value	RR	<i>P</i> value
Age >69 years	1.04	0.0006	1.11	0.0003	–	NS	–	NS
Stage								
Ia/b/IIa vs.	1.53	0.0001	1.99	0.001	1.03	<0.0001	1.12	0.005
Ic vs. IIb vs. III								
LVSI positive	1.72	0.04	1.63	0.01	1.51	0.01	1.02	0.01
Lymphadenectomy (not performed)	1.08	0.02	1.75	0.02	1.13	0.01	1.09	0.01
Grade 3 histology	1.38	0.01	1.35	0.005	1.33	0.04	1.34	0.01

LVSI lymphovascular space invasion, OS overall survival, DFS disease-free survival, CSS cancer-specific survival, LRC locoregional control, NS nonsignificant, RR relative risk

bowel obstruction; she developed an acute abdomen requiring emergency surgery and died 1 week later. We registered two patients with severe chronic lymphedema, one of whom had severe intestinal toxicity requiring surgery. One patient had a radiation-induced sacral fracture. According to the RT technique, the 5-year Kaplan–Meier estimate of grade 3 or more toxicity was 0 % for VB alone, 6 % (95 % CI, 1–11) for helical Tomotherapy + VB, 9 % (95 % CI, 1–17) for 3D-EBRT + VB, and 22 % (95 % CI, 12–32) for 2D-EBRT + VB ($P = 0.002$; Fig. 1).

Second Cancers

In a follow-up period of 10–151 months, 24 patients (10 %) were diagnosed with second cancers after PORT. The 5- and 10-year estimated second-cancer incidence was 9 % (95 % CI, 5–13) and 23 % (95 % CI, 13–33), respectively, for the whole population. The 10-year estimated second-cancer rate was 19 % (95 % CI, 10–29) in patients younger than 60 years at diagnosis versus 15 % (95 % CI, 9–21) compared with those 60 years or more ($P = 0.46$). In 4 of 24 women, the malignancy was situated inside or in close proximity to the irradiated volume. The most common in-field second cancers were bladder ($n = 1$) and colorectal ($n = 3$) cancer. The most common out-of-field malignancy was breast cancer ($n = 12$). According to the RT technique, the 5-year estimated second-cancer incidence was 0 % for helical Tomotherapy, 5 % for 3D-EBRT (95 % CI, 1–9), 7 % for VB alone (95 % CI, 1–13), and 12 % (95 % CI, 4–20) for 2D-EBRT ($P = 0.01$).



Number at risk	0	24	48	72	96	120
2D-EBRT+VB (n=69)	58	46	34	24	13	
3D-EBRT+VB (n=51)	41	25	16	3		
Tomotherapy+VB (n=43)	32	6	2			

FIG. 1 Grade 3 or more late toxicity by radiotherapy technique. 2D-EBRT two-dimensional external beam radiation therapy, 3D-EBRT three-dimensional external beam radiation therapy, VB vaginal cuff brachytherapy

DISCUSSION

It is recognized that EBRT in patients with EC leads to better pelvic control compared with surgery alone. A favorable influence on survival, however, has failed to be shown in several randomized trials and meta-analyses.^{3–6,8} Therefore, the life expectancy of these patients should be taken into consideration to tailor adjuvant RT with the final aim of keeping good LRC while preventing RT-related side effects. Depending on the treatment technique, prognostic factors, and median follow-up time, in early stage disease LRR rates are in the range of 5–15 %.^{15,16} Our results compare well with the literature (14 %; 95 % CI, 9–19) and confirm good LRC with PORT (Table 4). Patients treated with VB alone had a 5-year LRC of 89 %. Well-selected high- to intermediate-risk patients according to the PORTEC-2 inclusion criteria had an LRC rate of 96 % at 5 years. These results are in line with those obtained in PORTEC-2, suggesting the feasibility of such an approach in an appropriately selected subgroup of patients.¹⁰ It is important to note that in the PORTEC-2 study, there was also a significant quality-of-life advantage for patients receiving VB alone.¹⁷ Serious complications in 3–5 % of patients after PORT have been reported in various randomized trials and, as in our patients, concerned mainly the gastrointestinal tract.^{3,4,6,9} In our study, severe complications were diagnosed in nearly 10 % of the patients. These higher-than-expected rates of severe late complications are in line with what is reported in other studies using EBRT + VB.¹⁸ We agree that the benefit of VB as a boost after EBRT is questionable.¹⁹ The increased incidence of injury to the bowel might be explained by the fact that after hysterectomy, the small-bowel loops occupy the place of the uterus, thereby receiving high doses of EBRT and remaining close to the VB source. We have recently abandoned the systematic use of the VB boost, offering this additional treatment only to patients with cervical invasion or positive vaginal margins. In our series, we showed that the change from 2D- to 3D-EBRT and to helical Tomotherapy significantly decreased the incidence of severe side effects. The use of IMRT for gynecologic cancers is still a matter of debate. The largest prospective study comparing non-IMRT versus IMRT showed a reduction in grade 3 or more long-term toxicity from 17 to 6 %.²⁰ Other retrospective series comparing 3D-EBRT versus IMRT after TAH-BSO have failed to show any benefit.²¹ A recent phase II feasibility trial by the radiation therapy oncology group reported a nonsignificant 12 % reduction in grade 2 or more bowel adverse events in patients treated with IMRT after TAH-BSO.²² A phase III randomized trial is warranted to confirm the potential benefits of IMRT in EC. In our series, the 5-year second-cancer incidence was 0 % for helical Tomotherapy, 5 % for 3D-EBRT, and 12 % for

TABLE 4 Randomized trials evaluating the role of adjuvant radiotherapy in endometrial cancer

Study	Eligibility	Arms	No of patients	LRR rate (%)	DFS rate (%)	OS rate (%)	Number of EC related deaths	Median follow-up (months)	Comments
Aalders et al. ^{4,11}	Stage I	VB + pelvic RT	260	2	88	89	28	>60	Lymphadenectomy required
Creutzberg et al. ^{5,14}	Stage I, G1, >50 % invasion; or G2 any invasion; or G3, <50 % invasion	VB alone Pelvic RT	277 354	7 6*	87 50	91 52	25 37	156	No lymphadenectomy
Keys et al. GOG 99 ³	G2/3 + LVSI + >2/3 myometrial invasion, >50 years of age with 2 of these features; or >70 years of age with any of these features	Observation Pelvic RT	361 190	15 1.6*	54 93	60 92	30 19	69	Lymphadenectomy required
ASTEC NCIC CTG EN5 ⁶	FIGO (1988) I or IIA with either G3 (serous included) or >50 % myometrial invasion	Observation Pelvic RT	452 453	3.2 6.1	85 86	84 84	37 41	58	Lymphadenectomy not required; VB given to 53% of the patients in the observation arm
Nout et al. PORTEC 2 ⁹	FIGO (1988) I or IIA & G1-2, >60 years, <50 % myometrial invasion; or G3 with <50 % myometrial invasion; or IIA, G1-2; or G3 <50 % invasion	Observation Pelvic RT VB	214 213	2.1 5.1	83 78	80 85	10 15	45	Lymphadenectomy not required
Sorbe et al. ⁷	FIGO (1988) stage I, endometrioid type and G1-2, or G3 with FIGO Ic (>50 % invasion), or aneuploidy	Pelvic RT + VB	224	1.5*	87	89	15	62	Lymphadenectomy not required (only sampling of enlarged lymph nodes)
Randall et al. GOG 122 ²³	FIGO III/IV, maximum residual disease <2 cm, no LVSI	VB alone WART + pelvis Chemotherapy (CAP)	223 202 194	5 NR NR	87 38 42	90 42*	27 100*	74	Node sampling optional
Susumu et al. ²⁵	FIGO (1988) Ic-IIc with >50 % myometrial invasion	Pelvic RT Chemotherapy (CAP)	193 193	7 7	84 82	85 87	21 13	60	96 % of patients had lymphadenectomy
Maggi et al. ²⁴	FIGO I/II with >50 % myometrial invasion, G3 or IIc, high risk histology excluded	Pelvic RT Chemotherapy (CAP)	166 177	11 14	63 63	69 66	9 10	95	Pelvic and lumbo-aortic node sampling

VB vaginal cuff brachytherapy, RT radiation therapy, LRR locoregional recurrence, DFS disease-free survival, OS overall survival, EC endometrial cancer, G grade, LVSI lymphovascular space invasion, FIGO international federation of gynecology and obstetrics, PORTEC the postoperative radiotherapy in EC study group, GOG gynecology oncology group, NCIC CTG EN5 national cancer institute of Canada clinical trials group EC trial 5, ASTEC a surgical trial in EC, WART whole abdominal radiation therapy, AP doxorubicin and cisplatin, CAP cyclophosphamide, doxorubicin, cisplatin

^a Differences between arms were statistically significant ($P < 0.05$)

2D-EBRT, keeping in mind the shorter follow-up in Tomotherapy patients. Onsrud et al.¹¹ analyzed the long-term outcome of a randomized trial of postoperative VB + EBRT versus VB alone. After a median follow-up of 20.5 years, women younger than 60 years treated with VB + EBRT had a significantly higher mortality rate due to second malignancies (hazard ratio, 2.02; 95 % CI, 1.3–3.1). It should be noted that the RT delivery in that study was performed mainly with cobalt-60 using a two-field technique. This technique fully exposes the bladder and the bowel to high doses of radiation. The 15-year rates of second cancers in the PORTEC-1 randomized trial were 22 % in patients treated with adjuvant EBRT versus 16 % in the observational group ($P = 0.10$). The incidence rates were compared with those of an age- and sex-matched population. The observed versus expected ratios were 1.40 for the total group (1.62 for EBRT and 1.2 for the observational group, P not significant). The predominant cancer types were gastrointestinal cancer (6.2 % in the EBRT group vs. 3.2 % in the observational group) and breast cancer (4.8 % in the EBRT group vs. 6.6 % in the observational group). These differences did not reach statistical significance.¹⁵ Chaturvedi et al.²³ reported on a series of 101,760 cervical cancer patients with more than 40 years of follow-up who were treated ($n = 52,613$) or not treated ($n = 27,382$) with RT. They observed 12,496 incidents of second cancers [standard incidence ratio (SIR) = 1.30, 95 % CI, 1.28–1.33]. Compared with the general population, the excess absolute risk was 22.7 per 10,000 person-years. Cervical cancer patients treated with RT as opposed to those not treated with RT were at increased risk of second cancers at any site, and the SIR was dependent on the amount of RT administered. Heavily irradiated organs located in the irradiated field and receiving >3 Gy (average radiation dose was 10–66 Gy depending on the location of the organ) had an SIR of 1.59 (95 % CI, 1.16–1.26), compared with moderately (1–3 Gy) and lightly (<1 Gy) irradiated sites (SIR = 1.30, 95 % CI, 1.54–1.66, and SIR = 1.21, 95 % CI, 1.16–1.26, respectively). This study demonstrates that the risk of RT-induced second cancers increases with time and that there is an RT dose effect.

Our study adds information to the ongoing discussion in prescribing adjuvant EBRT versus VB and the technology of EBRT. Nevertheless, because of its retrospective approach, it has several limitations. We could not obtain information regarding urinary incontinence or fecal leakage, which are well-known side effects particularly after EBRT and are better assessed in quality-of-life studies. Lymphadenectomy was heterogeneously performed. Finally, we believe that RT and chemotherapy should be considered for patients with locally advanced disease and those with clear-cell or serous-papillary histology on the basis of the high frequency of distant recurrence and LRR

observed.^{24–27} The role of chemotherapy in stage I–II disease with high-risk pathologic features is under evaluation in the ongoing PORTEC-3 trial.

CONCLUSION

For patients with high- or intermediate-risk EC, VB alone offers high rates of local control with no severe complications. EBRT should be tailored to patients with high-risk features because the possible severe late toxicity may outweigh the benefits. The addition of a VB boost after EBRT is associated with higher-than-expected late severe complications. The correlation between severe late toxicity and RT techniques is observed in our study. When EBRT is indicated, IMRT and daily image-guided RT should be considered as a viable treatment option to minimize severe late toxicity. Patients should be informed about the potential increased risk of second malignancies after the diagnosis of EC and PORT because 2D-EBRT techniques significantly increase the risk of second tumors and the severity of side effects. Longer follow-up and more patients are needed to confirm the lowest second cancer rates obtained with IMRT in this study. The potential benefits observed with IMRT should be confirmed in a randomized trial.

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CONFLICT OF INTEREST Authors declared no conflicts of interest.

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