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Survival after relapse in patients with endometrial cancer: results from a randomized trial☆

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Abstract

Objective. The aim of this study was to determine the rates of local control and survival after relapse in patients with stage I endometrial cancer treated in the multicenter randomized PORTEC trial.

Methods. The PORTEC trial included 715 patients with stage 1 endometrial cancer, either grade 1 or 2 with deep (>50%) myometrial invasion or grade 2 or 3 with <50% invasion. In all cases an abdominal hysterectomy was performed, without lymphadenectomy. After surgery, patients were randomized to receive pelvic RT (46 Gy) or no further treatment.

Results. The analysis was done by intention-to-treat. A total of 714 patients were evaluated. At a median follow-up of 73 months, 8-year actuarial locoregional recurrence rates were 4% in the RT group and 15% in the control group ($P < 0.0001$). The 8-year actuarial overall survival rates were 71 (RT group) and 77% (control group, $P = 0.18$). Eight-year rates of distant metastases were 10 and 6% ($P = 0.20$). The majority of the locoregional relapses were located in the vagina, mainly in the vaginal vault. Of the 39 patients with isolated vaginal relapse, 35 (87%) were treated with curative intent, usually with external RT and brachytherapy, and surgery in some. A complete remission (CR) was obtained in 31 of the 35 patients (89%), and 24 patients (77%) were still in CR after further follow-up. Five patients subsequently developed distant metastases, and 2 had a second vaginal recurrence. The 3-year survival after first relapse was 51% for patients in the control group and 19% in the RT group ($P = 0.004$). The 3-year survival after vaginal relapse was 73%, in contrast to 8 and 14% after pelvic and distant relapse ($P < 0.001$). At 5 years, the survival after vaginal relapse was 65% in the control group compared to 43% in the RT group.

Conclusion. Survival after relapse was significantly better in the patient group without previous RT. Treatment for vaginal relapse was effective, with 89% CR and 65% 5-year survival in the control group, while there was no difference in survival between patients with pelvic

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relapse and those with distant metastases. As pelvic RT was shown to improve locoregional control significantly, but without a survival benefit, its use should be limited to those patients at sufficiently high risk (15% or over) for recurrence in order to maximize local control and relapse-free survival.

Keywords: Endometrial carcinoma; Radiotherapy; Vaginal recurrence; Salvage treatment; Randomized trial

Introduction

Endometrial carcinoma, the most common gynecologic cancer, has a predominantly favorable outcome. This is mainly due to the fact that the majority of endometrial cancers are diagnosed at an early stage (75–80% stage 1). The cornerstone of treatment for patients with stage 1 endometrial cancer is total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO). If risk factors are present, that is, myometrial invasion to 50% or more of the myometrial width and/or grade 2 or 3 histology, pelvic radiotherapy (RT) is usually considered indicated in order to reduce the risk of vaginal and pelvic relapse.

The role of postoperative radiotherapy in the treatment of stage 1 endometrial carcinoma has remained controversial due to a lack of data from randomized studies and, moreover, to the low relapse rate after TAH-BSO and radiotherapy tailored to prognostic factors. Reported 5-year overall survival rates are 80–90%, cancer-specific survival rates 90–95%, and locoregional relapse rates 4–8%. Most locoregional relapses occur in the vagina, mainly in the vaginal vault. Retrospective studies showed complete remission rates after salvage treatment for isolated vaginal relapse to be 40–80% in previously unirradiated patients [1–10], compared to 10–25% in those who had previous RT [1,6,7]. In contrast, complete remission rates of pelvic relapse were low, ranging from less than 5% for patients who had previous pelvic RT to 5–30% in those not previously irradiated [5,8,9,11].

As the efficacy of postoperative radiotherapy for stage 1 endometrial carcinoma had never been established in a randomized trial, and in view of the expected efficacy of salvage treatment for vaginal relapse in previously unirradiated patients, a multicenter prospective randomized trial was done. The objectives of this trial, the PORTEC trial, were to establish the role of radiotherapy in stage 1 endometrial cancer and to compare locoregional control, overall survival, treatment-related morbidity, and the efficacy of salvage treatment after relapse in patients treated with surgery alone or with surgery and pelvic radiotherapy.

The main results of the PORTEC trial have previously been reported [12]. This analysis presents an update of the results with 8-year survival and relapse rates and focuses on the efficacy of salvage treatment for relapse and the comparison of the study groups with respect to the vaginal, pelvic, and distant relapse rates and survival after relapse.

Materials and methods

Patient selection and treatment

Patients were eligible for the PORTEC trial if they had a stage 1 endometrial carcinoma, either grade 1 or 2 with deep (50% or more) myometrial invasion or grade 2 or 3 with less than 50% myometrial invasion. Surgery consisted of TAH-BSO without lymphadenectomy. After surgery, patients were randomized to receive postoperative pelvic RT or no further treatment.

Radiotherapy was administered to the pelvic region according to a standardized protocol [12]. The target volume consisted of the previous site of the uterus and adnexa, the parametria, the proximal two-thirds of the vagina, and the lymphatic drainage regions along the iliac vessels up to the promontory. The superior field border was specified at the L5–S1 disc. The total dose to be delivered to this volume was 46 Gy using 2-Gy daily fractions.

Patients were evaluated every 3 months for the first 3 years, every 6 months during the 4th and 5th years, and then annually. At each follow-up visit, a history was obtained and pelvic examination was done. A chest radiograph was obtained once a year. Vaginal smears or biopsy samples were taken on indication. Appropriate diagnostic procedures (biopsy, abdominal CT scans, chest radiography) were performed whenever a recurrence was suspected. If an isolated recurrence was diagnosed, treatment with curative intent was initiated, unless precluded by patient or disease factors. After treatment for relapse, patients were again evaluated every 3 months for the first 3 years and every 6 months thereafter. Failure after treatment for relapse was specified as second vaginal, pelvic, and/or distant relapse or death without second failure.

Statistical methods

The analysis was by intention-to-treat and patients were analyzed according to the treatment arm to which they were assigned. All randomized patients were included in the analysis, except for one patient who had to be excluded because all information on treatment and outcome was missing. Patterns of failure were recorded by the sites of failure: vaginal, pelvic, distant, or both. Locoregional failures were defined as vaginal or pelvic recurrences or both. Combined vaginal and pelvic recurrences were scored as pelvic, and if both distant and locoregional recurrences were detected, the failure type was distant metastases. Competing

risk analysis was applied to calculate competing risks of first failure split by site of failure and of risk of death split by cause of death. If the cause of death was unknown, but occurred after relapse, or if there was any doubt about a possible recurrence, the cause of death was considered endometrial carcinoma ($n = 5$). If in a patient without relapse the cause of death could not be established with full certainty but was considered by the treating physician as most likely cardiovascular (e.g., sudden death), the death was scored as intercurrent ($n = 6$).

The observed numbers of secondary cancers and deaths were compared with those expected on the basis of Dutch sex-specific and age-specific incidence rates of cancer and death [13,14] by the use of the subject-years method. Relative incidence rates (RIR) were calculated as the ratio of observed and expected numbers of secondary cancers or deaths.

The Kaplan–Meier method, log-rank test, and Cox regression analyses were used for time-to-event analyses with the following endpoints: locoregional recurrence from randomization with censoring at the date of last contact, or death in case of no locoregional recurrence; relapse from randomization with time of failure at the first date of relapse and censoring at the date of last contact or death in case of no relapse; overall survival from randomization with failure defined as death irrespective of the cause and censoring at the date of last contact for patients still alive; survival after relapse from the first date of relapse with failure defined as death irrespective of the cause and censoring at the date of last contact for patients still alive. All reported P values are based on two-sided tests with $P < 0.05$ taken to be significant.

Results

A total of 715 patients were enrolled in the study. Of these, 354 patients were assigned to postoperative pelvic radiotherapy and 361 to no further treatment. A total of 714 patients could be evaluated. The study groups were well balanced for patient characteristics such as age and concurrent morbidity and histologic features [12]. Major protocol violations occurred in 21 (3%) patients. In the group assigned to RT, 15 did not receive it: 12 patients refused RT, 1 had major wound problems, and 2 patients died before RT could be initiated. In the group assigned to observation, 6 patients requested RT. These 21 patients were included in the present analysis, which was done on data frozen on October 1, 2001.

The median follow-up duration for the patients alive at the time of this analysis was 73 months (range 12–131 months, 1st and 3rd quartiles 53 and 98 months). For the patients with relapse, the median follow-up duration after the diagnosis of relapse was 44 months (range 1–117 months, 1st and 3rd quartiles 28 and 64 months).

Table 1
Outcome: 8-year actuarial rates of relapse, death, and second cancer

Outcome	Radiotherapy ($n = 354$)			Control ($n = 360$)		
	Number	8-year %	SE	Number	8-year %	SE
Locoregional relapse	**13**	**4.0**	**1.2**	**46**	**14.9**	**2.2**
Vaginal vault	5	1.5	0.6	21	6.7	1.5
Vagina	2	0.6	0.4	11	3.3	1.0
Pelvic	6	1.9	0.9	14	4.9	1.4
Distant metastasis	**30**	**10.1**	**1.9**	**21**	**6.3**	**1.3**
Death	**84**	**29.3**	**3.0**	**68**	**23.1**	**2.7**
Endometrial cancer	29	9.6	1.8	24	7.5	1.5
Locoregional relapse	3	1.1	0.7	6	2.0	0.8
Distant relapse	24	7.9	1.6	17	5.2	1.3
Complications	2	0.6	0.4	1	0.3	0.3
Secondary cancer	19	5.3	1.4	12	5.0	1.5
Other causes	36	14.4	2.4	32	10.6	2.0
First failure type	**92**	**31.1**	**3.0**	**97**	**31.5**	**3.0**
Vaginal relapse	7	2.0	0.7	32	9.5	1.7
Pelvic relapse	6	1.7	0.8	14	4.5	1.3
Distant metastasis	25	7.9	1.6	12	3.5	1.0
Death without relapse	54	19.5	2.7	39	14.0	2.3
Secondary cancer	**36**	**13.9**	**2.5**	**26**	**10.3**	**2.1**
GI tract	17	6.5	1.8	9	3.4	1.2
Breast	7	2.2	0.9	11	4.2	1.4
Other	12	5.3	1.7	6	2.7	1.1

Note. SE, standard error.

Outcome

The 8-year actuarial probabilities of relapse, causes of death, incidence of secondary cancers, and sites of relapse are shown in Table 1. Locoregional recurrences were diagnosed in 13 patients in the RT group and in 46 patients in the control group. The 8-year actuarial locoregional relapse rates were 4% in the RT group and 15% in the control group ($P < 0.0001$). There was no survival difference, with 8-year actuarial overall survival rates being 71% in the RT group and 77% in the control group ($P = 0.18$).

Most recurrences in the control group were vaginal (10% at 8 years), while in the radiotherapy group most relapses occurred at distant sites (8-year rate 10% compared to 6% in the control group, $P = 0.20$). Four patients (1 in the RT group, 3 in the control group) had a combined vaginal and pelvic relapse, and 9 patients (4 RT, 5 controls) had an isolated pelvic relapse. Seven patients (2 RT, 5 controls) had a vaginal and/or pelvic relapse simultaneously with distant metastases. In 5 cases (2 RT, 3 controls) a solitary distant metastasis was diagnosed.

The majority of the relapses occurred in patients with risk factors (Table 2). First failure analysis at 8 years showed that locoregional relapse as first event occurred mostly in patients over 60 years old and in those with grade 2 tumors with outer 50% myometrial invasion. In contrast, the risk of distant relapse was especially increased for patients with grade 3 tumors.

The median time to relapse was 21 months (range 3–108

Table 2
First failure analysis according to prognostic factors

	Number	Actuarial 8-year percentages		
		Locoregional relapse	Distant relapse	Death without relapse
Age				
<60	201	3.1	3.7	5.1
60–70	270	11.1	5.2	11.9
>70	243	10.9	8.0	31.7
Initial grade and invasion				
Grade 1, >50%	142	7.0	4.9	17.2
Grade 2, <50%	221	5.0	2.3	17.6
Grade 2, >50%	277	12.6	6.5	17.6
Grade 3, <50%	74	9.5	15.0	10.2
Revised grade and invasion				
Grade 1, <50%	115	4.4	3.5	14.3
Grade 1, >50%	226	6.9	5.8	21.4
Grade 2, <50%	81	4.9	6.2	14.7
Grade 2, >50%	103	14.8	8.0	7.3
Grade 3, <50%	44	13.8	13.9	11.2
Unknown	145	12.3	2.8	19.5

Note. Actuarial probabilities at 8 years.

months), with 60% of relapses diagnosed within 2 years and 76% within 3 years. Even though most relapses were detected within a few years, some patients had late relapses occurring more than 5 years after initial treatment. Late vaginal recurrences were diagnosed in 3 patients, at 85, 86, and even 107 months after initial treatment, respectively. Late distant metastases were found in 2 patients, at 78 and 80 months.

A total of 152 patients have died. The majority of deaths were due to intercurrent disease: 8-year actuarial rates of intercurrent death were 19.7% in the RT group and 15.6% in the control group ($P = 0.35$). Endometrial cancer related deaths, 9.6 and 7.5%, respectively ($P = 0.48$), were mainly due to distant metastases. Death due to locoregional disease progression occurred in 1.1% in the RT group and 2.0% in the control group. The RIR of death, as estimated by the ratio of observed and expected cases, was 1.61 in the RT group and 1.32 in the control group.

Secondary cancers were diagnosed in both treatment groups, but more frequently in the RT group. An excess incidence of secondary cancers was observed (62 patients, 36 in the RT group and 26 in the control group), compared with the expected number of secondary cancers ($n = 39.4$) based on a population with similar age and sex distribution and 3953 person-years. The RIR for all secondary cancers was 1.57 ($P = 0.0004$). The respective RIRs for colorectal cancer, for all cancers of the gastrointestinal tract (GI), and for breast cancer were 2.07 ($P = 0.005$), 2.32 ($P < 0.0001$), and 1.42 ($P = 0.14$). The majority of secondary cancers occurring in the RT group were colorectal cancers (RIR 2.72, $P = 0.016$), while breast cancer was the predominant type of secondary cancer in the control group (RIR 1.73, $P = 0.07$). The RIRs for all secondary cancers, for colorectal cancers, and for GI tumors were highest in the RT group, while the RIR for breast cancer was higher among the controls. These differences between the study groups were, however, statistically not significant.

Treatment for relapse

Vaginal relapse was diagnosed in 39 patients, 35 of whom could be treated with curative intent. One patient refused treatment, 1 patient died shortly after the diagnosis of vaginal failure (presumably due to a major stroke, but scored as endometrial cancer death in view of the uncertainty), and 2 patients were diagnosed with large vaginal recurrences for which no curative treatment could be given. In 31 (89%) of the 35 patients who had curative treatment a complete remission was obtained. In contrast, only 4 of 10 patients who were treated for pelvic relapse with curative intent reached a complete remission. Table 3 shows the types of treatment and the complete remission rates for vaginal and pelvic relapse.

At a median follow-up after relapse of 44 months, 24 (77%) of the 31 patients who had reached a complete remission after salvage therapy were still disease free. Five patients were diagnosed with distant metastases but remained locally controlled, while 2 patients had a second vaginal relapse after 3 and 4 years, respectively. Two of the 4 patients with pelvic relapse who reached a complete remission have remained progression free.

Table 4 summarizes the results of treatment for distant relapse. Four patients with solitary distant metastasis, in the lung, omentum, abdominal wall, and brain, respectively, were treated with local surgery followed by hormonal ther-

Table 3
Treatment for vaginal and pelvic relapse

	Vaginal relapse			Pelvic relapse		
	RT	Control	Total	RT	Control	Total
Total	7	32	39	4	9	13
None or palliative treatment	2	2	4	2	1	3
Treatment with curative intent	5	30	35	2	8	10
Radiotherapy	3	24	27	2	5	7
Surgery	—	2	2	—	1	1
Surgery + RT	2	3	5	—	—	—
Hormonal + RT	—	1	1	—	2	2
Treatment result						
Complete remission	5	26	31	—	4	4
No CR	—	3	3	2	4	6
Unknown	—	1	1	—	—	—
Further FU after CR						
NED	3	20	23	—	2	2
Distant relapse	2	3	5	—	1	1
Second vaginal relapse	—	2	2	—	—	—
Died without relapse	—	1	1	—	1	1

Note. Three patients with both vaginal and pelvic relapse counted as pelvic relapse. Seven patients with both pelvic and distant relapse were excluded. NED, no evidence of disease; CR, complete remission; FU, follow-up; RT, radiotherapy group; Control, control group.

Table 4
Treatment for distant relapse

Treatment type	Distant relapse		
	RT	Control	Total
Local radical	2	3	5
Radiotherapy	—	1	1
Surgery + RT	1	—	1
Surgery + hormones	1	2	3
Treatment result			
CR	2	3	5
No CR	—	—	—
NED after FU	1	3	4
Palliative	28	18	46
Radiotherapy	1	1	2
Hormonal therapy	10	7	17
Chemotherapy	4	1	5
Hormonal + RT	2	1	3
Surgery + hormones	1	1	2
No treatment	10	7	17

Note. CR, complete remission; FU, follow-up; NED, no evidence of disease; RT, radiotherapy group; Control, control group.

apy or radiotherapy. Three are still disease free after 1–5 years, while one (with brain metastasis) died due to widespread metastases after 2 years. A fifth patient was treated with local radiotherapy for a solitary bone metastasis and is alive without disease progression after 3 years. Most patients with multiple metastases were either treated palliatively with progestagens or did not receive treatment at all due to advanced age and rapid deterioration. There were no long-term survivors among these patients.

Survival after relapse

In view of the relatively small numbers of patients with relapse, especially in the RT group, and the shorter follow-up time after treatment for relapse, 3-year survival data after relapse are reported. Actuarial 3-year survival rates after any first relapse were 51% in the control group and 19% in the RT group ($P = 0.004$); see Fig. 1.

The 3-year actuarial survival rates after vaginal, pelvic, and distant relapse were 73, 8, and 14%, respectively (Fig. 2). The prognosis for patients with pelvic relapse was as poor as for those with distant metastases. The patients with solitary distant metastases had a relatively long disease-free survival after treatment.

Fig. 3 shows the survival after relapse for the RT and control groups separately. The actuarial 5-year survival rates after vaginal relapse were 43% in the RT group and 65% in the control group. This suggests that a substantial proportion of these patients may be cured. However, the number of patients at risk is too small to establish the long-term survival after vaginal relapse.

Discussion

In the randomized, multicenter PORTEC trial the vaginal, pelvic, and distant relapse rates after postoperative radiotherapy or no further treatment for stage 1 endometrial cancer were evaluated. The results show the clear difference between the study groups in the risk of vaginal and pelvic

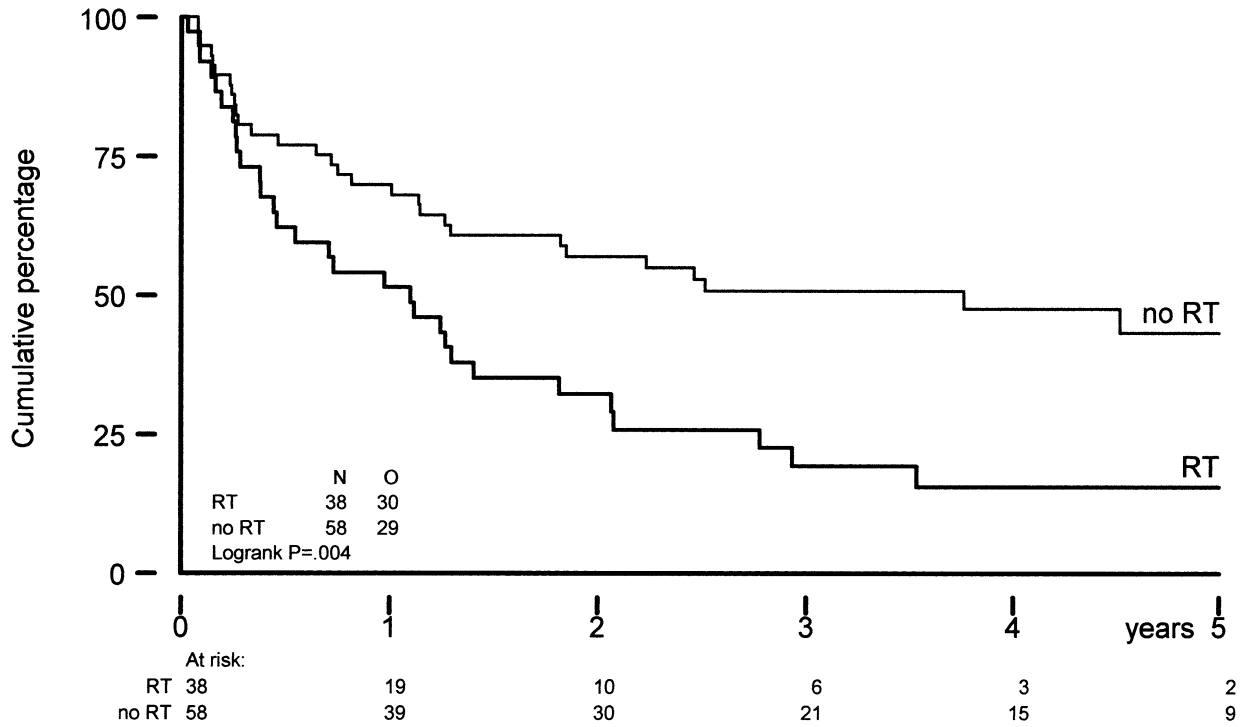

Fig. 1. Probability of survival after first relapse for patients assigned to postoperative radiotherapy (RT) or no further treatment (no RT).

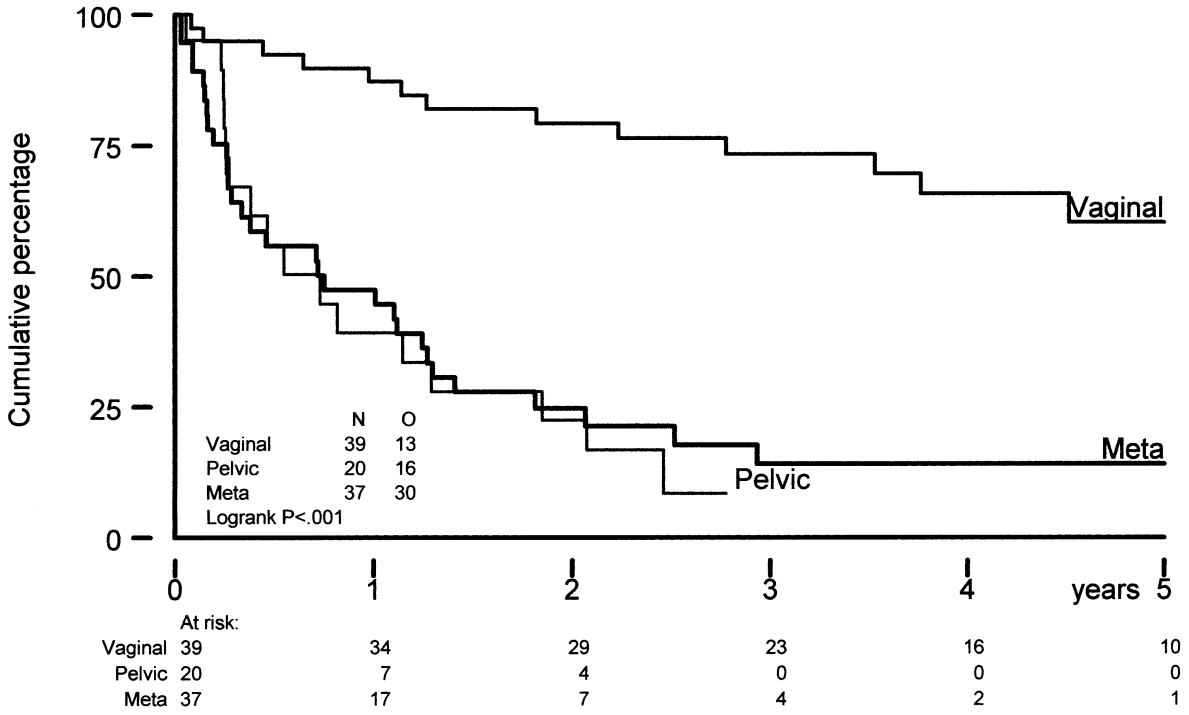

Fig. 2. Probability of survival after relapse by site of relapse: vaginal, pelvic, and distant relapse (both study groups combined).

relapse: 8-year actuarial locoregional recurrence rates were 4% in the RT group, in contrast to 15% in the control group ($P < 0.0001$). The higher locoregional control rate in the RT group did, however, not result in a survival benefit: 8-year actuarial overall survival rates were 71% in the RT group and 77% in the control group ($P = 0.18$). The failure-free survival rates at 8 years (failure defined as relapse or death without previous relapse) were 68.9 and 68.5%. The rate of distant metastases, being the major cause of endometrial-carcinoma-related death, was higher in the RT group than in the control group ($P = 0.20$).

An important factor to consider in order to explain this absence of a survival difference is the rate of successful salvage after treatment for relapse. From retrospective data it was expected that a significant proportion (40–80%) of patients with isolated vaginal relapse initially treated with surgery alone would be salvaged, while only a minority (5–30%) of patients with pelvic relapse would reach a complete remission. The present analysis was done to investigate whether these assumptions could be substantiated.

The median time to recurrence was 21 months. In most series, the median interval between diagnosis and recurrence was 15–17 months [1,10,11,15], while some authors reported a shorter median interval of around 1 year [3,5,8]. Pai et al. reported a median interval of 24 months [4]. The relatively long median interval of 21 months found in our study is probably due to the long follow-up and the inclusion of late relapses occurring more than 6 years after the initial diagnosis.

At a median follow-up duration of 44 months after relapse, survival rates after relapse were established. The 3-year overall survival after first relapse was 51% for patients in the control group, compared to 19% for patients in the RT group. For patients with isolated vaginal relapse treated with curative intent, the complete remission rate was 89%, and the actuarial 3-year survival was 73%. The outcome after pelvic and distant relapse was poor, with only 8 and 14% of patients surviving 3 years. These survival rates after relapse are in accordance with literature data from retrospective series. Due to the small numbers of patients in these series, and the different treatment approaches used, the survival rates vary. Reported local control rates after radical treatment for isolated vaginal relapse in previously unirradiated patients range from 80–90% in patients with recurrences confined to the mucosa to 60–70% in those with more advanced disease. Overall survival rates at 5 years are around 40–50% [2–5,9,10,16]. Jereczek-Fossa et al. [8] found a lower survival rate of 25% at 5 years, probably due to a larger proportion of advanced pelvic relapses in their series. In patients previously treated with pelvic radiotherapy, lower survival rates after vaginal relapse of around 10–20% [6,11] have been reported. Most, if not all, deaths after pelvic or distant relapse are due to endometrial cancer, while a substantial proportion of deaths after treatment for vaginal relapse are due to intercurrent disease [1].

Factors determining the prognosis after treatment for relapse are the size and stage of the recurrence, the initial histology and grade, the interval between initial diagnosis and recurrence, the RT dose, the use of a brachytherapy boost, and the initial treatment [3,6,8,10,17,18]. Because of

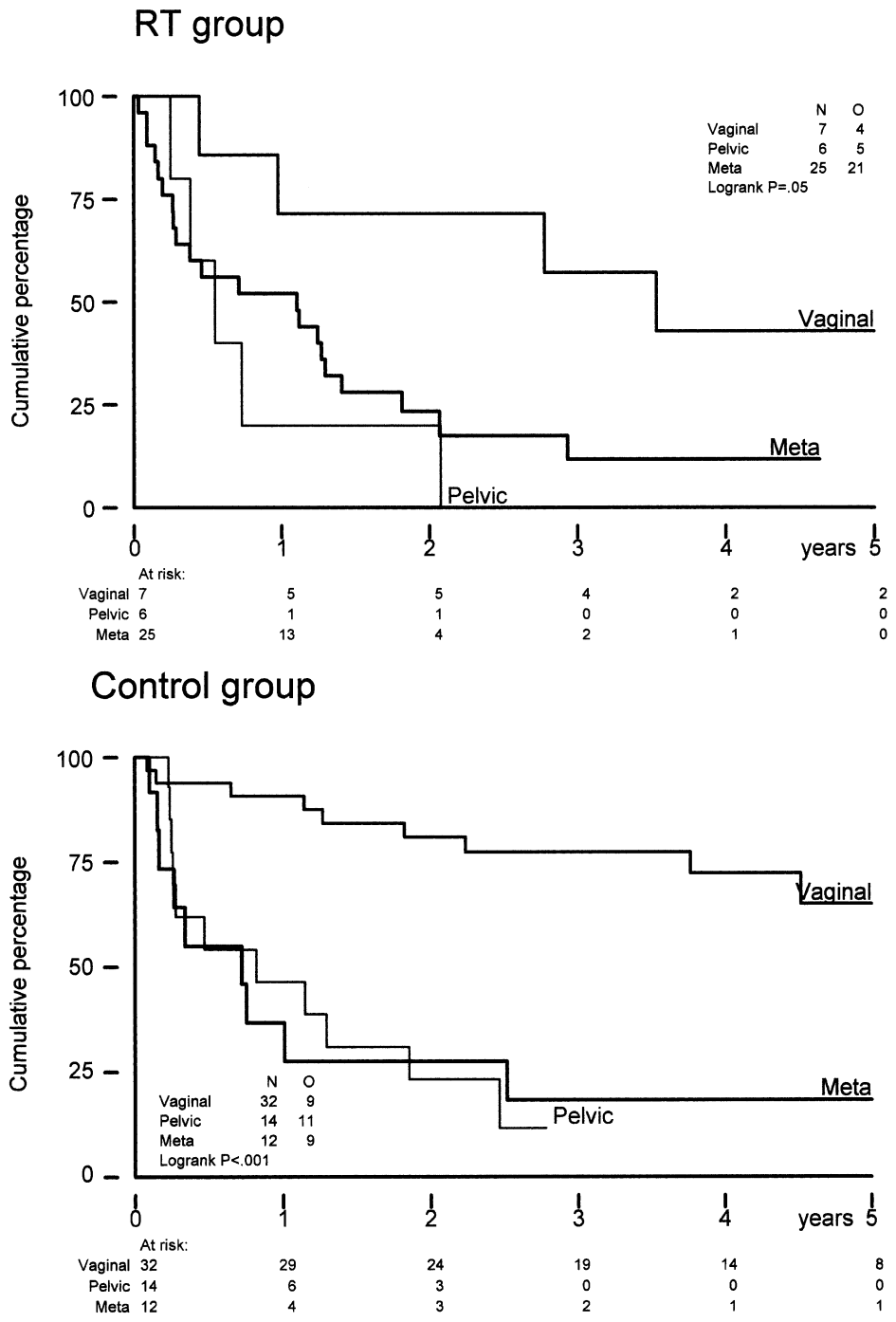

Fig. 3. Probability of survival after relapse by site of relapse for patients assigned to postoperative radiotherapy (RT group) and for patients assigned to no further treatment (control group).

the prospective randomized setting of our trial the only factor which differed between the two groups was the initial treatment. In the control patients treated with surgery alone, full RT for vaginal relapse was effective with 89% complete remission and 65% 5-year survival, compared to 43% 5-year survival among the patients assigned to RT. It should be kept in mind that, in the trial setting, patients were followed closely and many vaginal recurrences were diagnosed at an early stage. Especially the late recurrences were more often advanced tumors for which curative treatment was not possible.

Corn et al. [19] analyzed the relationship between local and distant failure for endometrial cancer and found that women with local failure had a nearly fourfold risk of distant failure compared to those who remained locally controlled. They speculated that local failure may be a cause

of, as well as a marker for, distant spread. However, their patients were all treated with postoperative RT. Our results show that despite the increased rate of locoregional recurrence in the control group, the rates of distant metastases were similar and even higher in the RT group. This suggests that the most aggressive cancers have already spread to distant sites before the initiation of RT and that the locoregional relapses do not by themselves cause subsequent distant spread. Distant failure seems to reflect inherent tumor aggressiveness. The results of ongoing trials must be awaited to see whether the addition of adjuvant chemotherapy in high-risk cases will reduce the rates of distant spread. Recently, the frequency of follow-up examinations and their value in detecting asymptomatic recurrences have been subject of discussion [15,20–22]. It was argued that the majority (50–75%) of women with relapse were symptomatic and that regular follow-up is not cost effective as patients with relapse can only occasionally be salvaged. Shumsky et al. [22] proposed a risk-based follow-up scheme in which low-risk patients are followed by their family physician. However, in patients with early stage disease treated with surgery alone, salvage treatment is effective and these patients should be followed closely to diagnose vaginal relapse at the earliest possible, usually asymptomatic, stage. Regular evaluations including visual inspection of the vagina and bimanual rectovaginal exams (taking Pap smears or biopsies only on indication) are sufficient to diagnose vaginal recurrence at an early stage. As distant relapse can only very occasionally be treated with a view to a long symptom-free interval, it cannot be recommended to actively screen for distant metastases outside the scope of clinical trials.

The excess incidence of second cancers in our series was not unexpected, as the association of endometrial cancer with other adenocarcinomas, in particular breast cancer and colorectal cancer (whether or not as part of Lynch type 2 syndrome), is well known [23]. As patients with a previous malignancy were not eligible for the PORTEC trial, we only report secondary cancers diagnosed after the treatment for endometrial cancer. Apart from the increased incidence of colorectal cancer and breast cancer, we found an excess incidence of GI tract cancers in general (including colorectal cancers and cancers of the gallbladder, liver, bile ducts, pancreas, stomach, and anus). The incidence rates of colorectal cancers and of GI cancers were significantly increased in the RT group, while breast cancer was the predominant type of secondary cancer in the control group. These differences were, however, not statistically significant. In their population-based series of patients with endometrial carcinoma, Re et al. [23] found RIRs for subsequent breast cancer of 1.71 and for colorectal cancer of 1.48, compared to 1.42 and 2.07 in our study. Re et al. suggested common etiologic factors in these cancers, including similar predisposing genetic mutations and environmental factors.

In conclusion, postoperative radiotherapy for stage 1 endometrial cancer significantly increases local control, but has no impact on survival. Salvage therapy for isolated vaginal recurrence, the main site of recurrence in the control group, is effective with a complete remission rate of 89% and actuarial 5-year survival of 65% in the control group. Therefore, the use of postoperative RT should be limited to the group of patients at sufficiently high risk of locoregional recurrence (15% or over) to warrant the risk of treatment-associated morbidity in order to maximize initial local control and relapse-free survival. In the PORTEC trial, the patients at intermediate to high (greater than 15%) risk were found to be those with at least two of the three following major risk factors: age 60 or over, deep (outer 50%) myometrial invasion, and grade 3 histology [12]. In the randomized GOG 99 trial, which has until now only been published as an abstract [24], patients with stage 1–2 endometrial cancer were randomized after TAH-BSO with lymphadenectomy to receive pelvic radiotherapy or no further treatment. Interestingly, the results are strikingly similar to those obtained in the PORTEC study: 88% 2-year relapse-free survival in the control group (17 locoregional recurrences in 200 patients) and 96% in the RT group (3 recurrences in 190 patients) and mainly vaginal recurrences in the control group. However, the rate of severe complications as related to the combined use of surgical staging and external beam radiotherapy was 8%.

The goal of therapy for low- and intermediate-risk endometrial cancer should be to minimize treatment morbidity without compromising the high survival rates [25]. Patients at a low (less than 10%) risk of recurrence can be safely followed and treated only in case of relapse. For patients at intermediate to high risk (10–25%) it can be debated whether postoperative vaginal brachytherapy alone can be used in order to minimize vaginal recurrence while decreasing treatment-related morbidity [26–30]. A new trial, named PORTEC-2, has recently been initiated in The Netherlands to answer this question.

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