Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial

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Summary

Background Postoperative radiotherapy for International Federation of Gynaecology and Obstetrics (FIGO) stage-1 endometrial carcinoma is a subject of controversy due to the low relapse rate and the lack of data from randomised trials. We did a multicentre prospective randomised trial to find whether postoperative pelvic radiotherapy improves locoregional control and survival for patients with stage-1 endometrial carcinoma

Methods Patients with stage-1 endometrial carcinoma (grade 1 with deep [⩾50%] myometrial invasion, grade 2 with any invasion, or grade 3 with superficial [<50%] invasion) were enrolled. After total abdominal hysterectomy and bilateral salpingo-oophorectomy, without lymphadenectomy, 715 patients from 19 radiation oncology centres were randomised to pelvic radiotherapy (46 Gy) or no further treatment. The primary study endpoints were locoregional recurrence and death, with treatment-related morbidity and survival after relapse as secondary endpoints.

Findings Analysis was done according to the intention-to-treat principle. Of the 715 patients, 714 could be evaluated. The median duration of follow-up was 52 months. 5-year actuarial locoregional recurrence rates were 4% in the radiotherapy group and 14% in the control group ($p<0·001$). Actuarial 5-year overall survival rates were similar in the two groups: 81% (radiotherapy) and 85% (controls), $p=0·31$. Endometrial-cancer-related death rates were 9% in the radiotherapy group and 6% in the control group ($p=0·37$). Treatment-related complications occurred in 25% of radiotherapy patients, and in 6% of the controls ($p<0·0001$). Two-thirds of the complications were grade 1. Grade 3–4 complications were seen in eight patients, of which seven were in the radiotherapy group (2%). 2-year survival after vaginal recurrence was 79%, in contrast to 21% after pelvic recurrence or distant metastases. Survival after relapse was significantly ($p=0·02$) better for patients in the control group. Multivariate analysis showed that for locoregional recurrence, radiotherapy and age below 60 years were significant favourable prognostic factors.

Interpretation Postoperative radiotherapy in stage-1 endometrial carcinoma reduces locoregional recurrence but has no impact on overall survival. Radiotherapy increases treatment-related morbidity. Postoperative radiotherapy is not indicated in patients with stage-1 endometrial carcinoma below 60 years and patients with grade-2 tumours with superficial invasion.

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Introduction

Endometrial carcinoma is the most common gynaecological cancer, having an incidence in western countries of 15–20 per 100 000 women per year.[1] 75–80% of endometrial cancers are diagnosed at an early stage (International Federation of Gynaecology and Obstetrics [FIGO] stage I). The most significant prognostic factors are tumour stage, histological grade, and depth of myometrial invasion. Others are age, histological type, peritoneal cytology, vascular space invasion, progesterone receptor activity, menopausal stage, and uterine size.[2–13] Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the cornerstone of treatment. 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 is indicated to reduce the risk of pelvic relapse. The value of postoperative radiotherapy in the treatment of patients with stage-1 endometrial carcinoma is, however, controversial due to a lack of data from randomised studies and the low relapse rate.[14] Patients with stage-1 endometrial carcinoma treated with surgery and postoperative radiotherapy have a 5-year overall survival of 80–90%, a 5-year cancer-specific survival of 90–95%, and locoregional recurrence rates of 4–8%.[2,5,6,9,12,15–20] However, patients with grade-3 tumours with deep myometrial invasion have a much higher risk of relapse.[2,5–7,19] Only one randomised study has been reported, in which 540 women who had had postoperative vaginal radiotherapy were randomly assigned to additional pelvic radiotherapy or observation.[2] Although pelvic radiotherapy reduced vaginal and pelvic recurrence (2% *vs* 7%), more distant metastases were found in the pelvic radiotherapy group (10% *vs* 5%), and survival was not improved (89% *vs* 91% at 5-years). Only

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Characteristic	Radiotherapy (n=354)	Control (n=360)	Total (n=714)
Age (years)			
<60	93 (26)	108 (30)	201 (28)
60–70	136 (38)	134 (37)	270 (38)
>70	125 (35)	118 (33)	243 (34)
Mean (SD)	66·3 (9)	65·7 (9)	66·0 (9)
Range	41–85	43–90	41–90
Nulliparous	71 (20)	86 (24)	157 (22)
Diabetes	42 (12)	47 (13)	89 (12)
Hypertension	92 (26)	84 (23)	176 (25)
Histological diagnosis			
Adenocarcinoma	321 (91)	341 (95)	662 (93)
Adenoacanthoma	17 (5)	7 (2)	24 (3)
Adenosquam.carc.	8 (2)	4 (1)	12 (2)
Papillary serous ca.	1 (<1)	0 (0)	1 (<1)
Clear cell carc.	2 (<1)	2 (<1)	4 (<1)
Other	5 (1)	6 (2)	11 (2)
Myometrial invasion			
<50%	138 (39)	156 (43)	294 (41)
⩾50%	216 (61)	204 (57)	420 (59)
Histological grade			
1	74 (21)	68 (19)	142 (41)
2	245 (69)	253 (70)	498 (70)
3	35 (10)	39 (11)	74 (10)
FIGO stage			
IB grade 2	104 (29)	117 (32)	221 (31)
IB grade 3	34(10)	39 (11)	73 (10)
IC grade 1	74 (21)	68 (19)	142 (20)
IC grade 2	141 (40)	136 (38)	277 (39)
IC grade 3	1 (<1)		1 (<1)
Vascular space invasion	22 (6)	19 (5)	41 (6)

Data are number of patients (%), with the exception of mean age.

Table 1: **Patient characteristics**

the subgroup with grade-3 tumours with deep (⩾50%) invasion showed both improved local control and survival after additional pelvic radiotherapy.

In retrospective studies of stage-1 endometrial carcinoma treated surgically followed by radiotherapy in case of poor prognostic factors, relapse rates of 15–20% are reported, of which 4–7% are locoregional recurrences and 7–17% distant metastases.[5,6,9,12,15–21] Most locoregional relapses are in the vagina, mainly in the vaginal vault. In previously unirradiated patients the salvage rate for isolated vaginal relapse is 40–80%.[8,14,15,22–27] The salvage rate of extravaginal pelvic relapse is low, ranging from less than 5% for patients who have received previous pelvic radiotherapy to 20–30% in those not previously irradiated.[14,15,23,27,28] In the Gynaecological Oncology Group (GOG) staging study,[4] the risk of pelvic node metastases in surgical stage-1 endometrial carcinoma was less than 10%, except for the subgroup with grade-3 tumours, in whom the risk was 18%.

A multicentre prospective randomised trial was initiated to establish the role of postoperative pelvic radiotherapy in FIGO stage-1 endometrial carcinoma, based on the following rationale: the locoregional relapse rate of stage-1 endometrial cancer is low; the efficacy of radiotherapy has never been established in a randomised trial; lymphadenectomy studies[4,29] show an incidence of pelvic lymph node involvement in surgical stage-1 endometrial carcinoma of less than 10%; the salvage rate of vaginal relapses in previously unirradiated patients is high. Patients with grade-1 tumours with deep myometrial invasion, grade-2 tumours with any invasion, or grade-3 tumours with superficial invasion were randomly assigned to either postoperative pelvic radiotherapy or no further treatment. The objectives of the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) study were to compare locoregional control, overall survival, and treatment-related morbidity of patients with stage-1 endometrial carcinoma, treated with postoperative pelvic radiotherapy or surgery alone.

Methods

Patient selection and eligibility criteria

All but one of the 20 radiation oncology centres in the Netherlands took part. The patients were evaluated and treated by their local gynaecologist, most often a general gynaecologist with special interest in gynaecological oncology. Initial evaluation included a pelvic examination, and endometrial curettage with separate endocervical and endometrial sampling. Preoperative evaluation included a medical history and physical and pelvic examination, chest radiography, complete blood count, and blood-chemistry tests. An abdominal computed-tomography scan was optional. At the time of surgery, a median laparotomy was done and, after obtaining a peritoneal cytology specimen, abdominal exploration with careful palpation and biopsy of any suspicious lymph nodes or lesions was done. A total abdominal hysterectomy and bilateral salpingo-oophorectomy was done, without routine lymphadenectomy. The diagnoses of endometrial carcinoma, of the histological grade, histological subtype, and depth of myometrial invasion were made by the regional pathologist. Vascular space invasion and perineural invasion were noted if present. FIGO 1988 staging[30] was assigned on the basis of surgical and pathological findings.

Women of any age with a histologically proven endometrial adenocarcinoma (also including adenocarcinoma with squamous features, adenocarcinoma not otherwise specified, adenosquamous carcinoma, papillary serous carcinoma, and clear-cell carcinoma), postoperative FIGO stage I, grade 1 with deep (⩾50%) myometrial invasion, grade 2 with any invasion, or grade 3 with superficial (<50%) invasion were eligible for the study. While peritoneal cytology was recommended, patients were not excluded if this had not been done. All patients had a WHO-performance score of 0–2. Patients were excluded if they had a history of invasive cancer (except for basal cell carcinoma of the skin), and if they had previously received chemotherapy, hormonal therapy, or radiotherapy. The interval between surgery and radiotherapy had to be less than 8 weeks. Informed consent was obtained from all patients.

The protocol was approved by the Protocol Review Committee of the Dutch Cancer Society and by the medical ethics committees of the University Hospital Rotterdam/Daniel den Hoed Cancer Centre (DDHCC) and of the participating centres.

Study design and randomisation

Primary endpoints were locoregional recurrence and overall survival. Secondary endpoints were treatment morbidity and survival after relapse. The trial was designed with a minimum of 600 patients. This number gave a power of 98% for the detection of a difference on the locoregional recurrence rates of 10% (based on an expected locoregional recurrence rate in the radiotherapy group of 5%) with a two-sided test at significance level $\alpha=0{\cdot}05$, and a power of 86% for a 10% difference in overall survival at 5 years (85% in the radiotherapy group *vs* 75% in the control group). We decided it would be best to have many patients to increase the power for the detection of a smaller difference in survival, and the power of subgroup analyses.

Central blocked randomisation by telephone was done at the DDHCC trial office with variable block sizes and stratified by radiation oncology centre and depth of myometrial invasion (<50% *vs* ⩾50%).

Statistical methods

The analysis was by intention-to-treat and patients were analysed according to the treatment arm to which they were assigned. All randomised patients were included in the analysis, except for one patient who had to be excluded because all information on

treatment and outcome was missing. Patients who did not meet the eligibility criteria (n=10) or patients with protocol violations (n=31) were included in the analysis. The Kaplan-Meier method, log-rank test, and Cox-regression analysis were used for time-to-event analyses with the following endpoints: locoregional recurrence from randomisation with censoring at date of last contact or death in case of no locoregional recurrence; relapse from randomisation with time of failure at the first date of locoregional relapse or metastasis and censoring at the date of last contact or death in case of no relapse; and overall survival from randomisation with failure defined as death irrespective of the cause and censoring at the date of last contact for patients still alive.

Competing risk probabilities of failure were calculated with the following competing risks of first failure type: locoregional recurrence, distant metastasis, and death without previous relapse. If both distant metastases and locoregional recurrence were detected, the failure type was distant metastases. Competing risk analysis was also applied to calculate probabilities of risk of death split by cause of death and locoregional recurrence split by type of recurrence (vaginal vault, vaginal, or pelvic). Combined vaginal and pelvic recurrences were scored as pelvic.

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[1,31] by the use of the subject-years method.

The following prognostic factors were considered in the analysis: age, depth of myometrial invasion, and histological grade according to the diagnosis of the local pathologist. Since young age is a favourable prognostic factor,[2,6,13,20,32,33] especially age below 60 years,[13] age (at randomisation) was classified beforehand in three groups (<60, 60–70, and >70). The differences between the treatment groups in risk of locoregional relapse or death were tested with the log-rank test without adjustment for prognostic factors, and with the likelihood-ratio test in Cox-regression analysis with adjustment for age, depth of myometrial invasion, and grade. The treatment groups were compared with respect to the incidence of late complications with Pearson's χ^2 test. This analysis was not done according to intention-to-treat, but restricted to patients treated according to the assigned treatment arm. All reported p values are based on two-sided tests with $p<0{\cdot}05$ taken to be significant.

Radiotherapy

Postoperative radiotherapy was administered to the pelvic region according to a standardised protocol. 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 internal 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, 5 days a week. The radiation was delivered by anteroposterior and posteroanterior parallel ports, or a three-field technique, or a four-field box technique (anteroposterior, posteroanterior, and two lateral fields). The radiation dose was specified at the patient's midplane (for anteroposterior-posteroanterior fields), or at the isocentre of the fields. Dose homogeneity requirements were according to the criteria of the International Commission on Radiation Units and Measurements.

Follow-up

Patients were assessed every 3 months for the first 3 years, every 6 months during the fourth year and fifth years, and then annually. At each follow-up visit, a history was obtained with special emphasis on treatment-related morbidity, and physical and pelvic examination was done. A chest radiograph, and blood count and chemistry tests had to be obtained once a year. Vaginal smears or biopsy samples were taken on indication. Locoregional recurrences were confirmed by a biopsy sample. Follow-up information was provided through the data managers at the regional cancer centres, and additional information was obtained, if needed, from the radiation oncologists and gynaecologists involved. In case of locoregional recurrence, metastases, death, or secondary cancer, full documentation was obtained. After treatment for relapse, patients were again evaluated every 3 months for the first 3 years. Patterns of failure were recorded by the sites of failure: locoregional, distant, or both. Locoregional failures were defined as vaginal or pelvic recurrences, or both. Distant failures included para-aortic lymph-node metastases, abdominal relapses, liver, lung, bone metastases, and diffuse metastatic disease. Treatment complications were recorded and graded according to the Franco-Italian glossary.[34]

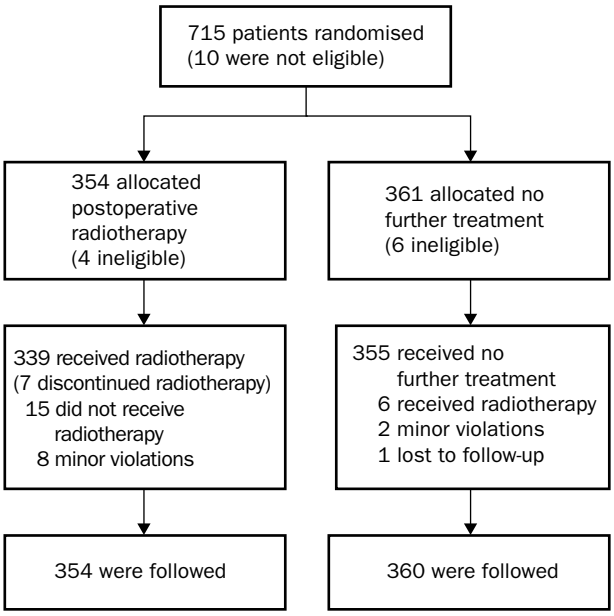


Figure 1: **Trial profile**

Pathology review

Staging and randomisation of the patients were done on the basis of the original pathology report. A central review of the pathology was done. To date, the histopathological slides of 567 (79%) patients have been reviewed and a histological diagnosis of endometrial carcinoma has been confirmed in all patients. The histological grade was found according to the FIGO 1988 grading criteria,[30,35] in contrast to the more subjective assignment of grade by the regional pathologist. Systematic grading of the specimens according to these criteria led to the assignment of grade 1 to significantly more tumours than in their previous pathology diagnoses: 60% of the tumours were grade 1; 32% grade 2, and 8% were grade 3, in contrast to the initial assignment of 21% grade 1, 68% grade 2, and 11% grade 3.

Results

715 patients with stage-1 endometrial carcinoma were enrolled in the study between June, 1990, and December, 1997. 354 patients were randomly assigned to postoperative pelvic radiotherapy and 361 to no further treatment. 714 patients could be evaluated (figure 1)

The study groups were well balanced for characteristics such as age and concurrent morbidity and histological type and grade and myometrial invasion (table 1). Ten patients (four in the radiotherapy group, six in the control group) were ineligible (1%). Three patients had a previous malignancy (two breast cancers and one gastric cancer); in four patients a full pelvic lymphadenectomy had been done; two patients had (minimal) stage 2A disease but were considered stage 1 at entry, and one patients had stage 1C grade-3 disease. These ten patients, except one, were treated according to the assigned treatment arm and were included in the analysis.

Outcome	Radiotherapy (n=354)			Control (n=360)		
	Number	5-year %	SE	Number	5-year %	SE
Locoregional relapse	11	4·2	1·3	40	13·7	2·1
Vaginal vault	5	1·6	0·7	19	6·4	1·4
Vagina	2	0·7	0·5	11	3·8	1·2
Pelvic	4	2·0	1·0	10	3·4	1·1
Distant metastasis	24	7·9	1·7	20	7·0	1·6
Death	57	19·3	2·7	48	14·9	2·2
Endometrial cancer	23	9·2	2·0	18	6·0	1·4
Locoregional relapse	3	2·0	1·1	4	1·1	0·6
Distant metastasis	18	6·4	1·6	13	4·5	1·3
Complications	2	0·8	0·6	1	0·3	0·3
Secondary cancer	11	3·4	1·2	8	1·9	0·8
Other causes	23	6·7	1·6	22	7·0	1·6
First failure type						
Locoregional relapse	11	3·9	1·2	40	13·1	2·0
Distant metastasis	19	5·5	1·3	11	4·1	1·3
Death without relapse	35	10·4	2·0	26	7·5	1·6
Secondary cancer	22	8·2	1·9	23	8·0	1·8
GI-tract	9	3·4	1·2	8	2·6	1·0
Breast	5	1·5	0·8	9	3·0	1·1
Other	8	3·3	1·4	6	2·4	1·1

GI-gastrointestinal.

Table 2: **Outcome**

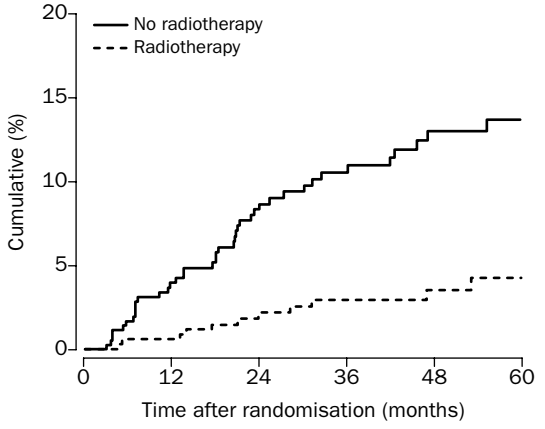
The analysis was done on data frozen on July 1, 1999, with date of last contact for 73% of the patients alive in the previous 12 months and for 27% in the previous 24 months. Three patients emigrated at follow-up durations of 32, 33, and 35 months. They were included in the analysis and censored at the date of last follow-up information. The median follow-up was 52 months.

Protocol compliance

31 (4%) protocol violations were recorded: 23 in the radiotherapy group and eight in the control group. Major protocol violations occurred in 21 (3%) patients. In the group assigned to radiotherapy, 15 patients did not receive it: 12 patients refused radiotherapy, two patients died before radiotherapy could be initiated (one died of presumed morphine intoxication, the other of diabetic coma), and one patient had major wound problems (necrotising fasciitis and multiple wound abscesses). In the group assigned to observation, six patients asked to receive radiotherapy. Other protocol violations in ten patients included a non-protocol radiotherapy dose/fractionation scheme in six patients, a split of 1 week during radiotherapy in one patient, a non-protocol treatment field length in one patient, and in two cases a violation of the surgical protocol (one patient had a vaginal hysterectomy, and in one patient part of the cervix had been left).

Radiotherapy

Radiotherapy was delivered according to the protocol in 324 (96%) patients and with (minor) deviations in 15 (4%) patients. The median number of days between randomisation and initiation of radiotherapy was 14 days (range 2–52 days, interquartile range 9–21 days). The median interval between the operation and the first radiotherapy session was 42 days (17–93, 32–50). In 41 (12%) patients this interval turned out to have been longer than 56 days; these patients were not counted among the protocol violations. The median duration of radiotherapy was 32 days (SD 4), and the mean total dose was 46 Gy (range 10–48, SD 3). The median energy used was 10 MV photons (range 2–25). The radiotherapy technique consisted of anteroposterior-posteroanterior fields in 101 patients, a four-field box technique in 177 patients, and a three-field technique in 61 patients.



Numbers at risk

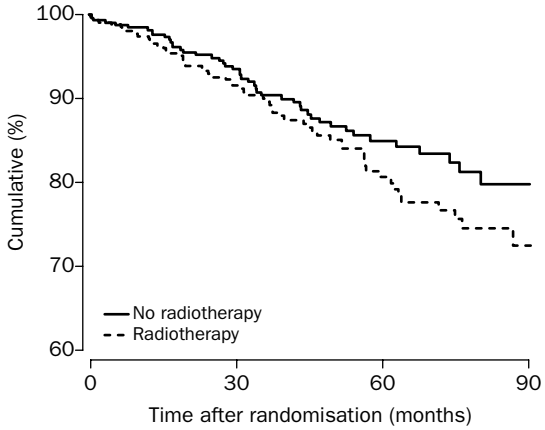
Radiotherapy	354	338	284	219	161	109
No radiotherapy	360	328	271	210	159	115

Figure 2: **Probability of locoregional (vaginal or pelvic) relapse for patients assigned to postoperative radiotherapy or no further treatment**

During radiotherapy, 63% of the patients were treated with medication or dietary measures, or both, for treatment-related symptoms. These symptoms occurred in 64%, 67%, and 60% respectively, of the patients treated with parallel opposed fields, 3-field and 4-field techniques (p=0·56). Acute complications, leading to a discontinuation of radiotherapy after doses of 10–44 Gy due to (perceived) toxicity, occurred in seven (2%) patients.

Adverse effects

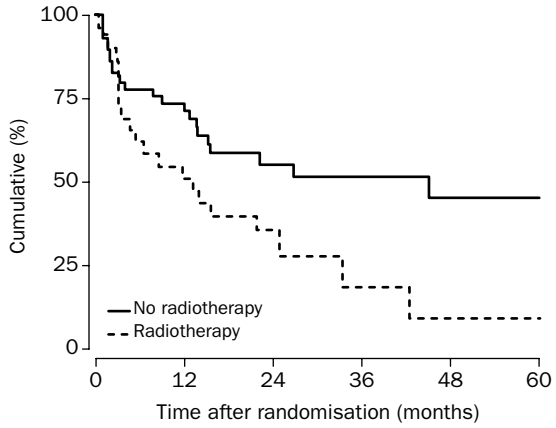
Late complications of the primary treatment were reported in 106 (15%) patients: 84 (25%) in the radiotherapy group, and 22 (6%) in the control group (p<0·001). Most of the complications were grade 1 (68%). In the radiotherapy group, late toxicity occurred in 26% of patients treated with parallel opposed fields, and in 22% of the patients treated with 3-field or 4-field



Numbers at risk

Radiotherapy	354	260	111	24
No radiotherapy	360	257	125	23

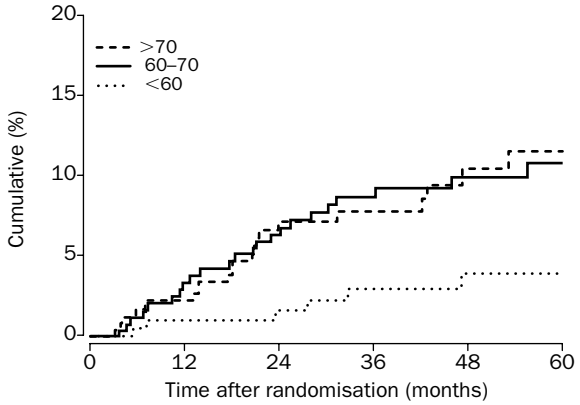
Figure 3: **Probability of survival for patients assigned to postoperative radiotherapy or no further treatment**



Numbers at risk

Radiotherapy	30	14	9	2	1	1
No radiotherapy	51	32	16	10	5	3

Figure 4: **Probability of survival after first relapse for patients assigned to postoperative radiotherapy or no further treatment**



Numbers at risk

<60	201	188	163	129	102	66
60–70	270	252	213	165	130	92
>70	243	226	179	135	88	66

Figure 5: **Probability of locoregional (vaginal or pelvic) relapse according to age group**
6 observed <60 years; 24 observed 60–70 years; 21 observed >70 years.

techniques (p=0·41). In the patient group aged below 60 treated with radiotherapy, late morbidity was reported in 25%, compared with 17% between 60 and 70 and 28% in the group over 70 (p=0·14). Most complications were of the gastrointestinal tract. Grade-3 complications occurred in 7 patients: in four patients small-bowel symptoms (subileus, obstruction) needed surgical intervention, with persisting abdominal symptoms afterwards (such as abdominal cramps, frequent bowel movements, or episodes of diarrhoea). Three patients had a sigmoid stenosis, for which sigmoid resection was done. Two of these patients had symptomatic diverticular disease as well. Six of these seven grade-3 complications occurred in the radiotherapy group (2%). In one patient an acute grade-4 complication was reported—this patient had Crohn's disease, and radiotherapy had to be discontinued at a dose level of 18 Gy due to an exacerbation of the disorder, of which she died a month later.

Pathology review

In order to discover if the histological grade assigned at the pathology review had more discriminatory power to predict relapse, a comparison was made between the histological grade assigned by the regional pathologist and the grade assigned at pathology review with respect to the risk of relapse. This analysis was restricted to all samples with complete pathology review, and was done with Cox-regression analysis including the factors age, depth of myometrial invasion, and treatment arm. The revised grade had no better predictive power than the original grade (details not shown) and since the patient eligibility was based on the grade assigned by the regional pathologist, we used the original grade as a prognostic factor in the analysis reported here.

Outcome

Table 2 shows the actuarial 5-year probabilities of survival and relapse, the causes of death, and the incidence of secondary cancers, by treatment group. Locoregional (vaginal or pelvic, or both) recurrences were diagnosed in 11 patients assigned to radiotherapy and in 40 patients assigned to observation. 5-year locoregional recurrence rates were 4% in the radiotherapy group and 14% in the control group (log-rank test, p<0·001; figure 2). Most recurrences were restricted to the vagina (73%). Five patients had distant metastases simultaneously with locoregional relapse, while nine patients developed metastases some time after locoregional relapse. The overall incidence of distant metastases was similar in the treatment groups: 8% in the radiotherapy group and 7% in the control group. In most cases the metastases were found at multiple sites, often involving the abdomen or the lungs, or both.

105 patients died, of whom 57 had been assigned to radiotherapy and 48 to observation. Overall survival at 5 years was 81% in the radiotherapy group and 85% in the control group (log-rank test, p=0·31; figure 3). 41 deaths were related to endometrial cancer: 31 patients died of metastatic disease, seven of progressive locoregional disease, and three of treatment-related complications. One patient died during the primary treatment (the patient with Crohn's disease): another patient died from septic shock during chemotherapy for metastases, and the third died of pulmonary embolism after laparotomy for resection of a pelvic recurrence. For four patients with relapse or suspected relapse the cause of death could not be firmly established. These deaths were judged to be related to endometrial cancer, and are included in the numbers above—endometrial-cancer-related death rates were 9% in the radiotherapy group and 6% in the control group (p=0·37). Most deaths were not related to endometrial cancer: 19 patients died due to a secondary cancer and 45 died from other causes, mainly cardiovascular. The 64 deaths not related to endometrial cancer accords with the

	Locoregional relapse		Death due to endometrial cancer	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Age ≥60	3·2 (1·3–7·5)	0·003	3·1 (1·2–8·0)	0·02
Invasion ≥50%	1·8 (0·9–3·8)	0·11	1·9 (0·8–4·4)	0·16
Grade 1	0·77 (0·4–1·6)	0·50	0·45 (0·2–1·3)	0·15
Grade 3	2·2 (0·8–5·8)	0·11	4·9 (1·9–12·5)	0·0008
No radiotherapy	3·9 (2·0–7·6)	<0·0001	0·76 (0·4–1·4)	0·37

Hazard ratio describes relative hazard of failure per unit time, for age ≥60 years compared with <60 years; for myometrial invasion ≥50% compared with <50%; for grade 1 and 3 compared with grade 2; for no radiotherapy compared with postoperative radiotherapy.

Table 3: **Cox-regression analysis**

expected death rate of 69·1 in a population with a similar age and sex distribution and 2916 person-years.

The incidence of secondary cancers was similar in both treatment groups; most were cancers of the gastrointestinal tract. There was an excess of secondary cancers (observed 48, expected 29·7) but an association of endometrial adenocarcinoma with other adenocarcinomas, especially of the gastrointestinal tract, is well known.

The observation that the higher incidence of locoregional recurrences in the control group is not reflected in the overall survival can be explained by the post-relapse survival. 23 of 51 patients with a locoregional relapse died, of whom only seven died due to their locoregional recurrence. By contrast, 21 of 30 patients with distant metastases as first failure died, of whom 19 died from the metastases. Salvage treatment of vaginal relapse was often successful. After vaginal recurrence, the 2-year survival was 79% in contrast to 21% after pelvic or distant relapse. At 3 years the survival was 69% and 13%, respectively ($p<0·001$). Figure 4 shows the survival after first relapse by treatment arm. The survival rate was better for patients in the control group than for patients in the radiotherapy group ($p=0·02$).

Prognostic factors

The risk of locoregional relapse was small for patients younger than 60 (4% *vs* 10%, $p=0·02$, figure 5), as was the risk of death from endometrial cancer (4% *vs* 9%). Grade-3 histology with less than 50% invasion was associated with a risk of locoregional recurrence similar to tumours of grade 1 or 2 with 50% or greater invasion (10%), but with a higher risk of distant metastases (14% *vs* 1% and 5%, respectively). For patients with grade-2 histology, deep myometrial invasion was associated with a higher risk of locoregional recurrence than superficial invasion (11% *vs* 5%, $p=0·05$), without a difference in risk of distant metastases (4% and 5%). The risk of death due to endometrial cancer was highest (16%) for patients with grade-3 histology.

Multivariate analyses showed the locoregional relapse rate to be threefold higher for patients aged 60 and over compared with those below this age ($p=0·003$), and almost fourfold higher for patients in the control group compared with the radiotherapy group ($p<0·0001$, table 3). Histological grade and depth of myometrial invasion did not reach significance as prognostic factors for locoregional recurrence, possibly due to the relatively small subgroups. Still, deep myometrial invasion compared with less than 50% invasion was associated with a relative risk of 1·8 ($p=0·11$), and grade-3 histology compared with grade 2 with a relative risk of 2·2 ($p=0·11$). The risk of endometrial-cancer-related death was significantly higher for patients aged 60 and over (hazard ratio 3·1, $p=0·02$) and for patients with grade-3 tumours (4·9, $p=0·0008$). After adjustment for age, grade, and depth of invasion there was no evidence of any benefit of radiotherapy for endometrial-cancer-specific survival ($p=0·37$)—the risk of death was even slightly lower in the control group (0·76).

Discussion

Our results show that postoperative radiotherapy improves locoregional control—but this improvement did not translate into a survival benefit. Overall 5-year survival was 85% in the controls and 81% in the radiotherapy group. The proportion of patients who suffered an endometrial cancer-related death was larger in the radiotherapy group (9% *vs* 6%, p=037). Survival rates in both groups accorded with data from retrospective studies[2,5,6,9,12,13,15–20] of stage-1 endometrial carcinoma treated with surgery and postoperative radiotherapy tailored to prognostic factors. It has often been stated that, because the patients who were selected for adjuvant radiotherapy were those at highest risk of relapse, retrospective studies would not be able to show a survival advantage for radiotherapy. The fact that low-risk patients treated with surgery alone have survival figures roughly similar to the high-risk group given radiotherapy has led investigators to postulate a survival benefit. However, this prospective randomised study shows no such survival benefit, with the implications that most patients with locoregional relapse are salvaged, and that the higher rate of locoregional relapse in the control group does not by itself cause a higher rate of distant relapse.

Most locoregional relapses were located in the vagina, mainly in the vaginal vault. This is a favourable location for salvage therapy with external and intracavitary radiotherapy, surgery, or both. Indeed, 75% of patients with locoregional relapse could be treated with curative intent, of which 85% reached a complete remission. The 2-year survival after vaginal relapse was 79% and the 3-year survival 69%, in contrast to 21% and 13% 2-year and 3-year survival after pelvic or distant relapse. The survival after relapse was significantly better for patients in the control group ($p=0·02$).

While locoregional relapse occurred predominantly in the control group, the rate of distant metastases was similar in both groups. This suggests that the subgroup of aggressively metastasising cancers has already spread to distant sites before the initiation of radiotherapy. The data further suggest that the locoregional relapses do not by themselves cause subsequent distant spread.

An important question remains: would a large proportion of the locoregional relapses observed in our control group have been prevented if vaginal brachytherapy had been given? Theoretically, if vaginal brachytherapy were 100% effective, this might have spared most (30 out of 40) of the locoregional relapses. However, in reports on patients treated with pre-operative or postoperative vaginal radiotherapy, vaginal recurrence rates vary from 2% to 7%.[2,8,16,29] In our (external) radiotherapy group the rate of vaginal relapse was 2·3%, compared with 10·2% in the control group. With an assumed vaginal relapse rate after brachytherapy of 5%, the reduction of vaginal relapse would be 5%, without any survival benefit. It can be debated whether this small reduction would justify treating all patients postoperatively with brachytherapy, especially as salvage treatment in case of locoregional relapse may be less effective if vaginal radtiotherapy has previously been given.

Various risk groups of stage-1 endometrial carcinoma have been defined on the basis of the major prognostic factors histological grade and depth of myometrial invasion. However, the definitions of low risk and high risk (and in some studies intermediate risk) categories are not unequivocal.[6,14–16,32] Tumours of grades 1 and 2 with superficial myometrial invasion are usually regarded as low risk, but depth of invasion is set either at less than 33% or less than 50% of the myometrial width, and for high risk categories either at 50% or more or 66% and

over. We used the 50% cutoff point according to the FIGO staging system. In these risk categories tumours of grades 1 and 2 are grouped together, because the difference in prognostic significance between grade 1 and grade 2 is small. The prognostic significance of grade in stage-1 endometrial carcinoma is less that that of age and myometrial invasion.[36] Furthermore, the assignment of the histological grade, especially the distinction between grades 1 and 2, is subject to variation between pathologists. In the study by Taylor and colleagues,[37] two gynaecological pathologists independently reviewing 85 hysterectomy specimens had a difference of opinion by at least one grade in 26% of the specimens. In view of the clinical limitations of a grade-2 pathological finding, they proposed a two-tiered grading system, which would improve both the reproducibility and the prognostic significance of the tumour grade. These findings explain why in our study the revised grade (with a considerable shift from grade 2 to grade 1) had no better predictive power than the original grade.

In our study, the subgroup with superficially (<50%) invasive grade-2 tumours had a locoregional relapse risk of 5% at 5 years, which was significantly lower than the risk of 10% for the other subgroups. The prognostic factors grade-3 histology and deep myometrial invasion were both associated with a twofold higher relative risk of locoregional relapse (p=0·11 in the multivariate analysis). Grade-3 histology was the strongest predictive factor for endometrial-carcinoma-related death. For locoregional control, however, the most significant prognostic factors were pelvic radiotherapy and patient age. A significant difference between patients below 60 and 60 and over was found. Age below 60 was also associated with a significantly lower risk of endometrial-carcinoma-related death. The fact that younger patients, especially those younger than 60, have a significantly better prognosis has been observed by others as well.[2,3,6,13,20,32,33] However, this has never resulted in specific treatment recommendations for this category.

There is controversy about the extent of the surgical procedure in stage-1 endometrial carcinoma. A routine staging lymphadenectomy is often recommended[3,29,38–40] for clinical stage-1 patients. However, the role of lymphadenectomy is unclear. Some authors claim a survival benefit, because they found a higher endometrial-cancer-specific survival rate than in reported series of patients treated with total abdominal hysterectomy and pelvic radiotherapy on indication.[29,39] In these retrospective studies, however, a selection bias was clearly present, because the patients were significantly younger than in other series. In the study by Mohan and colleagues[39] the mean patient age was 58, in contrast to 66 in our trial. Since age is a major prognostic factor, the survival benefit observed can be explained by the age difference. For surgical stage-1 patients, the risk of pelvic nodal metastases has been shown to be less than 10%.[4,29] Lymphadenectomy lengthens the operation time[29,41] and causes operative complications (ranging from infections, blood transfusions, and lymphocysts to leg oedema, deep-vein thrombosis, and bowel obstruction) that are claimed by most investigators to be minor, but do affect 18–22% of the patients.[7,39,40] The rate of complications is higher for patients who receive radiotherapy after lymphadenectomy.[7,21,33,42] Because its benefit is unclear, lymphadenectomy cannot be considered a standard procedure in stage-1 endometrial cancer patients.

The morbidity of pelvic radiotherapy should not be underestimated, either. The rate of serious (grades 3 and 4) complications is low. In our study, the rate of grade 3–4 complications in the radiotherapy group was 2%, which accords with published data.[5,17,21] However, some patients (20%) have longterm symptoms, mainly urgency, frequent bowel movements, abdominal cramps, and occasional bouts of diarrhoea, which are usually rated as mild (grade 1), but which do influence their quality of life. Most of the adverse effects observed in our study, as well as all serious (grade 3) complications, were of the gastrointestinal tract. The preponderance of gastrointestinal symptoms after external radiotherapy is a common observation.[5,17,21,33] Bladder toxicity other than minor incontinence, frequency, or episodes of cystitis did not occur.

In absence of a survival benefit, the purpose of adjuvant pelvic radiotherapy would be the prevention of uncontrolled pelvic disease, and the prevention of the stress and morbidity of the diagnosis and treatment of a locoregional relapse. Such an adjuvant treatment would only be indicated if the risk of recurrence after surgery alone is sufficiently high (in oncology usually >10% or >15%), and if the risk of uncontrolled pelvic disease after salvage treatment is high. It should therefore be selectively used in those subgroups of endometrial carcinoma at highest risk of relapse. A trade-off between the risk of locoregional recurrence and the survival rate after salvage treatment on the one hand, and the morbidity and cost of adjuvant pelvic radiotherapy on the other, has to be made for each subgroup of stage-1 endometrial carcinoma. For patients with superficially invasive grade-2 tumours, and for patients younger than 60 (except for deeply invasive grade-3 carcinomas, since these were not included in the study), adjuvant radiotherapy does not seem to be indicated, as the risk of locoregional relapse is 5% or less. Omitting radiotherapy in the grade-2 group with superficial invasion has been advised by other investigators[15,32] as well. In the "high risk" category of patients 60 and over with deeply invasive grade 1–2 tumours or superficially invasive grade-3 tumours, the locoregional relapse rate was 5% in the radiotherapy and 18% in the control group. The rates of distant metastases (6% and 5%) and of endometrial-cancer-related death (11% and 8%) were similar with and without radiotherapy. In view of the locoregional relapse risk without radiotherapy of over 15%, more mature results regarding the survival after relapse have to be awaited before reconsidering the indication for radiotherapy for this "high risk" group. Patients who do not receive postoperative radiotherapy should be followed closely, especially in the first 3 years, to diagnose and treat a locoregional recurrence at the earliest possible stage.

Contributors

C L Creutzberg, W L J van Putten, P C M Koper, and M van Lent designed the trial. C L Creutzberg coordinated the study. M L M Lybeert, J Jobsen, C C Wárlám-Rodenhuis, K A J de Winter, L C H W Lutgens, A C M van den Bergh, and E van de Steen-Banasik contributed to the accrual. W L J van Putten was responsible for the statistical analysis. H Beerman conducted the pathology review. C L Creutzberg and W L J van Putten prepared the first draft of the paper to which everyone then contributed.

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