PORTEC-4a:

Randomised Phase III Trial of molecular profile-based versus standard recommendations for adjuvant radiotherapy for women with early stage endometrial cancer

An international InterGroup trial

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Approval status:
KWF-CKS: UL2011-5336
CME LUMC: P16.054

Trial Registries:
Netherlands Trials Registry: NTR5841
ISRCTN Registry: ISRCTN11659025
Clinicaltrials.gov: NCT03469674

Version:
V2.4, 12 June 2018

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1. STUDY SYNOPSIS

Title	PORTEC-4a: Randomised Phase III Trial of molecular profile-based versus standard recommendations for adjuvant radiotherapy for women with early stage endometrial cancer.
Study Design	Prospective, multicenter, randomized Phase III trial led by the Dutch Platform for Radiation Therapy for Gynecological Tumors and the Dutch Gynaecologic Oncology Group
Primary Study Objective:	Establish and compare the rates of vaginal relapse in patients with high-intermediate risk endometrial carcinoma, treated after surgery with molecular risk profile based recommendations (investigational arm) for no additional treatment (55%), vaginal brachytherapy (40%) or external beam radiotherapy (5%), or with vaginal brachytherapy (standard arm; 21 Gy in 3 fractions) . Primary endpoint: vaginal recurrence
Secondary Study Objectives:	Establish and compare the rates of adverse events, patient-reported symptoms and quality of life, pelvic and distant recurrence, recurrence-free and overall survival, 5-year vaginal control (including treatment for relapse if applicable), and EC-related healthcare costs.
Inclusion Criteria FIGO 2009:	Histologically confirmed endometrioid type endometrial carcinoma, FIGO 2009 stage I, with one of the following combinations of stage, grade, age, and LVSI: 1. Stage IA, grade 3 (any age, with or without LVSI) 2. Stage IB, grade 1 or 2 and age $\geq$60 years 3. Stage IB, grade 1-2 with documented LVSI 4. Stage IB, grade 3 without LVSI 5. Stage II (microscopic), grade 1 WHO-performance status 0-2 Written informed consent
Exclusion Criteria:	Any other stage and type of endometrial carcinoma Histological types serous carcinoma or clear cell carcinoma (at least 10% if mixed type), or undifferentiated or neuroendocrine carcinoma Uterine sarcoma (including carcinosarcoma) Previous malignancy (except for non-melanomatous skin cancer) < 5 yrs Previous pelvic radiotherapy Interval between the operation and start of radiotherapy exceeding 8 weeks
Number of centres:	Unlimited; centres can join the ongoing study after authorization
Number of patients:	450 (including a pilot phase of 50 patients)
Planned duration	4-5 years of recruitment

2. INTRODUCTION

2.1 Endometrial carcinoma, risk groups and radiotherapy trials

Endometrial cancer (EC) is the most common gynaecological cancer and primarily affects postmenopausal women between 60 and 85 years of age. Many patients have concurrent comorbidities, such as obesity, diabetes, and cardiovascular diseases. Annual incidence rates in Western countries range between 15 and 25 per 100.000 women; incidence in The Netherlands is 22-23 per 10^5/year (ESR 16-17 per 10^5/year); about 1950 patients are diagnosed each year.[1]

The large majority of patients are diagnosed at early stage (International Federation of Gynecology and Obstetrics (FIGO) stage I, Appendix A[2]), due to early occurrence of symptoms. Surgery, consisting of total abdominal or laparoscopic hysterectomy and bilateral salpingo-oophorectomy (TH-BSO) is the primary treatment. Major risk factors are: stage, age, histological type, grade, depth of myometrial invasion and presence of lymph-vascular space invasion (LVSI).

Adjuvant RT for endometrial carcinoma has increasingly been tailored to these risk factors. Based on staging studies and prospective and retrospective data, endometrial carcinoma has been classified as low-risk, intermediate risk and high-risk for lymph node metastases, early disease spread to the abdominal cavity and distant sites. Low-risk are patients with stage IA (i.e., with no or superficial (<50%) myometrial invasion) EC, grade 1 or 2, and endometrioid type histology. High-risk are patients with stage IB (i.e., with deep (≥50%) myometrial invasion) grade 3 EC; or stage II (macroscopic stage II or post-surgical microscopic stage II grade 2 or 3; grade 1 is generally considered high-intermediate risk); or stage III; or non-endometrioid histologies (all stages with myometrial invasion). All others are intermediate-risk EC; this group has further been refined with prognostic factors to define a high-intermediate risk (HIR) group.[3,4] The majority of patients with EC have low to low-intermediate (55%) or high-intermediate (30%) risk features; only 15% have high-risk EC. Five-year survival rates for patients with intermediate risk EC are 80-85%, with most of these patients dying of comorbid conditions; rates of endometrial cancer death are 8-10%.

For low-risk endometrial cancer standard treatment is surgery alone, with 95% probability of 5-year relapse-free survival. Four randomized trials have established the role of external beam pelvic radiotherapy (EBRT) in intermediate risk endometrial carcinoma, see Table 1.[3-6] The Norwegian trial, published in 1980, included 540 women with clinical stage 1 endometrial carcinoma.[5] After hysterectomy and postoperative vaginal brachytherapy (60 Gy to the mucosal surface), patients were randomly assigned to additional EBRT (40 Gy in 2 Gy fractions) or observation. Although additional EBRT reduced vaginal and pelvic relapse rates (2% at 5 years versus 7% in the control group), more distant metastases were found in the RT group (10% versus 5%), and survival was not improved (89% versus 91% at 5 years). The subgroup with grade 3 tumors with deep (>50%) myometrial invasion showed improved local control and survival after EBRT (18% versus 27% cancer-related deaths); however, there were too few patients in this category to reach significance.

In the first Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) trial, 715 patients with stage I endometrial carcinoma, grade 1 or 2 with deep (≥50%) myometrial invasion or grade 2 or 3 with superficial (<50% invasion) were randomized after TAH-BSO to receive EBRT (46 Gy in 2 Gy fractions) or no additional treatment (NAT).[4] The 10-year locoregional relapse rates were 5% in the EBRT group and 14% in the control group ($p < 0.0001$). There was no significant survival difference between the treatment arms, with 5- and 10-year overall survival rates of 81% and 68% (EBRT) vs 85% and 73% (NAT, $p=0.14$) and endometrial cancer-related death rates of 10% and 8% ($p = 0.47$).[7] Risk criteria for locoregional relapse were

grade 3, age older than 60 years, and deep (≥50%) invasion.

Five-year survival after any relapse was 12% in the RT group and 48% in the control group (p<0.001). This was due to the fact that 75% of locoregional relapses in the NAT group were located in the vagina. After vaginal relapse, 5-year actuarial survival was 64%; EBRT 38% vs NAT 70%, which shows the high salvage rates of vaginal relapse in patients not previously irradiated. In contrast, outcome after pelvic and distant relapse was poor, with only 11% 5-year survival.[8]

The GOG#99 trial included 392 evaluable patients with FIGO 1988 stages IB, IC, or IIA endometrial carcinoma of any histological grade, who were randomized after TAH-BSO and lymphadenectomy to receive pelvic EBRT (50.4 Gy in 1.8 Gy fractions) or NAT.[3] A high-intermediate risk group (HIR) was defined based on the prognostic factors age, histological grade, myometrial invasion, and the presence of lymph-vascular space invasion (LVSI). The HIR group (33% of the study population) had a 2-year incidence of relapse in the NAT arm of 27%, in contrast to 6% for the LIR group (67% of patients). RT resulted in similar hazard reductions for the HIR and LIR subgroups (58% and 54%), but in absolute terms, the differences were greater for HIR patients, with a reduction of 4-year cumulative relapse from 27% (NAT) to 13% (RT). There was no significant difference in 4-year overall survival: 86% for NAT and 92% for EBRT. The 2-year estimated vaginal and pelvic failure rate was 12% in the NAT group and 3% in the EBRT group, for a 58% hazard reduction by RT. These results are strikingly similar to those obtained in the PORTEC study without lymphadenectomy. However, the 4-year crude rate of severe complications in GOG-99 was 13% for patients who had received RT, compared to a 5-year actuarial rate of 3% in the PORTEC trial, which underlines the increased risk of toxicity when combining extensive surgery including lymphadenectomy with pelvic radiotherapy. In addition, GOG#99 has shown that the HIR factors are associated with increased risk of relapse, regardless of lymphadenectomy. GOG#99 and other studies have shown lymph-vascular space invasion to be strongly associated with risk of lymph node involvement, as well as relapse at distant sites and inferior outcome.[9,10]

In the pooled ASTEC and EN5 trials, 905 patients with stage I endometrial carcinoma with risk features (deep invasion or high grade) were randomly allocated to EBRT or NAT.[6] There was no difference in overall survival (84% at 5 years in both groups), confirming the results of the PORTEC and GOG#99 trials. In the ASTEC/EN5 trial, brachytherapy was used at discretion of the centers and was used in both arms. As a consequence, 51% of the patients in the NAT arm received vaginal brachytherapy. This can explain the fact that the 5-year rates of isolated (not total) vaginal or pelvic recurrence were rather low in both arms: 6.1% in the NAT arm, and 3.2% in the EBRT arm (hazard ratio 0.46, p-0.02).

Conclusions that can be drawn from these randomized trials of EBRT in stage I EC are that EBRT provides a highly significant improvement of local control, but without survival advantage. Furthermore, mild adverse effects were recorded in 26% of EBRT patients in the PORTEC-1 trial, predominantly gastrointestinal (GI) toxicity[11]. A large proportion of endometrial cancer patients has a very favourable prognosis, and should be observed after TAH-BSO. Radiation therapy is a very effective salvage treatment for vaginal relapse in patients not previously irradiated. The use of postoperative RT should therefore be limited to the group of patients at sufficiently high risk of locoregional relapse to warrant the risk of treatment associated morbidity. In the PORTEC study, patients with two of the three major risk factors grade 3, age 60 or over, and outer 50% myometrial invasion, were found to have an increased risk of locoregional relapse, and to have the highest absolute benefit of pelvic RT. The 10-year locoregional relapse rates in this HIR group were 4.6% in the RT group and 23.1% in the control group.[7] In the GOG-99 trial, similar high risk criteria were identified, with reduction of isolated 4-year local relapse in the HIR group from 13 to 5%.

Because most relapses occur in the vagina, the use of vaginal brachytherapy alone has been advocated. Data from retrospective studies that used vaginal brachytherapy alone for stage I endometrial cancer have shown the 5-year risk of vaginal relapse to be 0% to 7%.[5,12-14] As pelvic and distant failure rates would not be reduced with brachytherapy alone, most studies included only or mainly low-risk patients (grade 1-2 with no or superficial invasion). However, the results of the randomized trials for intermediate risk EC suggested that, in view of the absence of survival benefit with EBRT and of the fact that most recurrences were located in the vagina, vaginal brachytherapy (VBT) might also be effective for patients with high-intermediate risk features to obtain local control with fewer side effects than EBRT and better quality of life. This was the rationale for the randomized PORTEC-2 trial (2002-2006), which compared EBRT and VBT among EC patients with high-intermediate risk features, both with regards to efficacy and health-related quality of life (HRQL).
In the PORTEC-2 trial, 427 patients with stage FIGO 1988 stages I-IIA endometrial carcinoma with high-intermediate risk features (i.e., age of at least 60 years, grade 1 or 2 tumors with outer 50% invasion or grade 3 with inner 50% invasion) were randomly assigned after surgery (TAH-BSO) to EBRT (n=214) or VBT (n=213). Quality of life was significantly better in the VBT arm. Patients who had brachytherapy reported better social functioning ($p<0.002$) and lower symptom scores for diarrhea, fecal leakage, the need to stay close to the toilet, and limitation in daily activities due to bowel symptoms ($p<0.001$). At baseline, after surgery, 15% of patients reported to be sexually active; this increased significantly to 39% during the first year ($p<0.001$). Sexual functioning and symptoms did not differ between the treatment arms.[15] Final results of the PORTEC2 trial confirmed the efficacy of vaginal brachytherapy. At median follow-up of 45 months, estimated 5-year rates of vaginal recurrence (VR) were 1.8% for VBT and 1.6% for EBRT ($p=0.74$).[16] Five-year rates of locoregional relapse (VR and/or pelvic recurrence, PR) were 5.1% and 2.1% ($p=0.17$). Only 1.5% vs 0.5% ($p=0.30$) presented with isolated PR; other PR were part of widespread disease relapse, while rates of distant metastases (DM) were similar (8.3 vs 5.7%, $p=0.46$). There were no differences in 5-year OS (84.8 vs 79.6%, $p=0.57$) and DFS (82.7 vs 78.1%, $p=0.74$). Rates of grade 1-2 gastrointestinal toxicity were significantly lower in the VBT group. Conclusions were that, in view of the similar efficacy of VBT with fewer side effects and better quality of life than EBRT, VBT should be the treatment of choice for EC patients with HIR features.[16]
Since the analysis and publication of the PORTEC-2 trial results, most international groups have started using VBT alone for patients with high-intermediate risk disease.
Pelvic EBRT is at present only recommended for patients with high-risk or advanced stage EC, for which it is an indispensible component of treatment, as shown in several prospective and retrospective studies.[17-20] In view of the increased risk of distant relapse and cancer related death, adjuvant chemotherapy is currently being investigated in several trials, such as PORTEC-3, and GOG#278.
First results of GOG#249 have been presented.[21] This trial included 601 patients with stage I-II EC with high-intermediate or high-risk factors, and compared VBT followed by 3 cycles of carboplatin-paclitaxel with pelvic EBRT. There were no differences in relapse-free survival (84 vs 82%) or overall survival (92 vs 93%) between the arms at a median follow-up of 24 months, and both arms were well-tolerated with high completion rates.

2.2. Vaginal brachytherapy in the PORTEC-2 trial

Based on literature data supporting the use of moderate-dose, convenient dose fractionation schedules for vaginal brachytherapy with high vaginal control rates (> 95%), and very low morbidity rates, dose schedules were chosen which would give an equivalent of 45-50 Gy to the mucosal surface of the upper half of the vagina. For the PORTEC-2 trial, both LDR and HDR were allowed as at the time LDR was still used at a

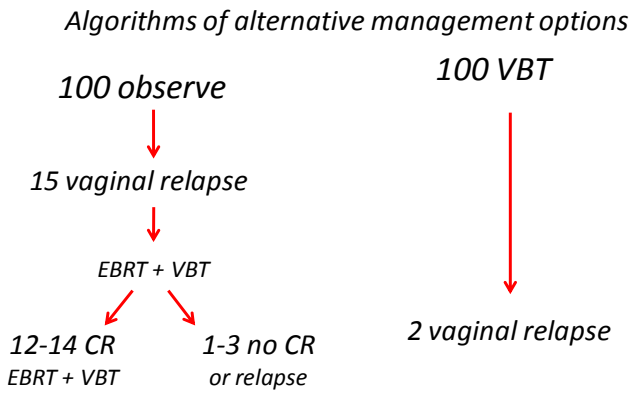
number of centres. Equivalent schedules allowed in PORTEC-2 were: LDR 30 Gy, specified at 5 mm depth, at a dose rate of 60-65 cGy/hr, in one session of 2-3 days, MDR 28 Gy, specified at 5 mm depth, at a dose rate of 100 cGy/hr, in one session of 28 h: and HDR 21 Gy, specified at 5 mm depth, in 3 fractions of 7 Gy each 1 week apart. The target length was the upper half of the vagina; it was recommended to choose the active length (prescribing at 5 mm depth) 1 cm shorter than the upper half of the vagina, resulting in the 100% isodose to cross the vaginal mucosal surface at 50% of the length.

In the PORTEC-2 trial, the HDR schedule was used in 80% of patients. The most commonly used active length was 40 mm. Vaginal control was excellent, with 1.8% vaginal recurrence at 5 years.

Although quality of life analysis did not show any differences in sexual functioning and symptoms between the EBRT and VBT groups in the PORTEC-2 trial, sexual activity in both groups was somewhat lower than in a reference population.[22] In the PORTEC-2 trial, the physicians recorded significantly more mild to moderate vaginal atrophy in the upper vagina in the VBT group: at 30 months, atrophy was reported in 40% of the patients in the VBT group; 18% grade 1 (mild atrophy) and 21% grade 2 (mild to moderate atrophy with teleangiectasia, but without narrowing or shortening of the vagina). Grade 3 mucosal toxicity (with narrowing or shortening) was rare: 1.9% in the VBT group, compared to 0.5 % in the EBRT group. Although these atrophic changes were apparently without consequences for vaginal and sexual functioning, the difference in atrophy compared to the EBRT group raises the question if the dose at the mucosa might be higher than necessary. In a study of dose specification either at 5 mm depth or at 3, 4 or 5 mm depth depending on physician's evaluation, results were similar and rates of toxicity lower in the individual dose specification arm.[23] Modern brachytherapy is image-guided and planning-CT scans allow individual planning of dose depth if bladder, rectum and bowel are within 2-3 mm of the cylinder surface.

2.3. Remaining questions

Criticism of the PORTEC-2 trial results has been that in view of the absence of survival advantage with RT and in view of the effective salvage probabilities of vaginal relapse, with 89% complete remission and 75% 3-year overall survival in PORTEC-1 trial patients who were treated for vaginal relapse in the control arm[24], that treating all patients with HIR features with brachytherapy is still significant overtreatment. If a watchful waiting policy would be adopted, with prompt treatment in case of vaginal relapse, the eventual local control (including treatment for relapse) might be very similar to the local control if brachytherapy was used for all cases.[25] See figure below.



Vaginal brachytherapy has only been compared to observation in one randomized trial including low risk patients (grade 1-2 with no or superficial invasion). The rate of vaginal recurrences was 1.2% in the

brachytherapy group (18-24 Gy in 3-6 fractions) versus 3.1% in the control group, p=0.11). Side effects were few and mild (grade 1-2).[26]

The estimated incidence of vaginal relapse in patients with intermediate or high-intermediate risk feature who are observed after surgery has also been confirmed in a Danish population study.[27] Among the 231 patients with intermediate-risk features the overall recurrence rate at 14 years was 21.6%, of which 14.3% were locoregional recurrences (9.5% vaginal and 4.8% pelvic), and 7.4% distant recurrences. For the 132 patients with high-intermediate risk disease these rates were 28.8% overall recurrence; 11.4% vaginal and 6.1% pelvic recurrence, and 8.3% distant metastases.

In a patient-preference treatment-trade off study among EC patients and health care professionals, the policy of vaginal brachytherapy (standard indication) was compared with a watchful waiting policy (only treating in case of relapse).[27] The minimally desired benefit of VBT was significantly lower for patients than for clinicians (median=0 vs 8%, P<0.001), for irradiated than for non-irradiated patients (median=0 vs 6.5%, P<0.001), and for radiation oncologists than for gynaecologists (median=4 vs 13%, P<0.001). The majority of patients chose vaginal brachytherapy in view of the low toxicity and high efficacy with the motivation to avoid the anxieties of relapsing disease and avoid more intensive treatment in case of relapse. Participants preferred the patient and clinician to share in the decision about VBT, rather than the clinician (or randomisation) to decide for them.

Despite the rationale for conducting a trial comparing standard vaginal brachytherapy for all patients with high-intermediate risk EC versus observation after surgery with prompt salvage treatment for the expected 15% of patients who will have local relapse, this design has not proven feasible in the first years of the PORTEC-4 trial. Only about 1 in 10-15 eligible women accepted randomisation and all of the others chose standard brachytherapy to have maximum probability of remaining relapse-free.

In a quantification study of lymph-vascular space invasion in tumor tissues of 924 patients who participated in the PORTEC-1 and -2 trials, it has become clear that especially substantial LVSI (in contrast to no LVSI or only focal LVSI) is a significant and strong risk factor, both for pelvic and distant relapse.[28] EBRT reduced the risk of pelvic nodal relapse among these EC with substantial LVSI who were otherwise high-intermediate risk.

With the recent developments of molecular risk profiling on endometrial cancers, more specific individual tumour-based risk profiles can be defined and a trial comparing standard brachytherapy to individual risk-based treatment recommendations has become most attractive.

2.4. Molecular risk factors of endometrial cancer

Much knowledge has been gained in the field of endometrial carcinogenesis by comparing molecular alterations of endometrioid (EEC, type I) with non-endometrioid EC (NEEC, type II, mainly serous), and pre-malignant with malignant lesions. In the last decades several unfavourable prognostic molecular alterations were identified, among which: loss of nuclear hormone (ER/PR) expression, *TP53* mutation, mutation of genes involved in the PI3K-AKT pathway (*PIK3CA, KRAS, PTEN*), altered Wnt-signaling (mutation of *CTNNB1* / nuclear accumulation of β-catenin) and L1CAM expression.[29-31] Most studies were retrospective and focused on single biomarkers in cohorts that were heterogeneous. They included combinations of low and high FIGO stages, NEEC tumors, and treatment was not controlled. For these reasons, their clinical utility remained unclear and promising molecular prognostic factors have not been implemented in the clinic up to now.

A major advance has been made by The Cancer Genome Atlas (TGCA) group that used an integrated genomic characterization with array based and sequencing techniques in a cohort of both EEC and NEEC (serous) tumors, including higher FIGO stages. TGCA defined four distinct EC subgroups: (1) *POLE*

ultramutated (good prognosis), (2) microsatellite instable hypermutated, (3) copy number low and (4) copy number high groups. The latter contains serous like, p53 mutated tumours with poor prognosis.[32] These four subgroups can be identified using a straightforward practical approach by analysis of their surrogate markers (POLE, MSI and p53).[33-35] Both POLE mutation as a favorable factor, and L1CAM expression as unfavorable factor have been confirmed and validated as reliable and significant prognostic molecular marker in tumor tissues from the combined PORTEC-1 and-2 trial cohorts.[33,36]

Within the KWF UL 2012-5447 grant entitled 'Improved risk assessment using molecular (epi)genetics to reduce over- and undertreatment in early stage endometrial cancer', these four subgroups and additional promising molecular markers were analyzed in tumor tissues of the combined PORTEC-1 and PORTEC-2 trial populations of >800 women with mostly (low)- intermediate or high-intermediate risk, and some with high-risk early stage endometrial cancer, to obtain an integrated molecular risk profile. Analysis of p53 expression, MSI status, *POLE* mutation, 159 hotspot mutation analysis of 13 genes (*BRAF*, *CDKNA2*, *CTNNB1*, *FBXW7*, *FGFR2*, *FGFR3*, *FOXL2*, *HRAS*, *KRAS*, *NRAS*, *PIK3CA*, *PPP2R1A,* and *PTEN*), protein expression of L1CAM, ARID1a, PTEN, ER, and PR was undertaken. These techniques proved to be highly feasible with a success rate of 96.8% for assignment in one of the subgroups. The so-called copy number low group was renamed No Specific Molecular Profile (NSMP) group, as it was hoped to find driving mutations in a number of cases among this group without a specific profile. In total 834 EECs could be classified: 74 (9%) p53-mutant, 219 (26%) microsatellite unstable, 49 (6%) *POLE*-mutant, and 492 (59%) NSMP, whereas 27 tumours (3%) were not classified because they presented with more than one classifying alteration (p53, MSI or *POLE*). Candidate molecular prognostic factors were selected through a process of uni- and multivariate analysis, in the presence of established clinicopathologic prognostic factors (age, grade, depth of myometrial invasion, grade of LVSI). In the first run, p53-mutation, >10% L1CAM and substantial LVSI were the strongest independent predictive factors for an increased risk of locoregional and distant recurrence and decreased overall survival. As expected, the majority of patients in this combined PORTEC-1 and -2 cohort (including 242 low risk patients), belonged to either the NSMP or MSI subgroup. Therefore a second run was performed after exclusion of patients with *POLE*-mutation (favorable) and p53-mutation or >10% L1CAM or substantial LVSI (unfavorable). In this second run, MSI was prognostic for distant recurrence and overall survival and *CTNNB1*-mutation for distant recurrence. Identical results were found when the analysis was restricted to patients with high-intermediate risk features confirmed by central pathology review. If ER and PR were negative this was an unfavorable factor in univariate analysis, but in multivariate analysis ER-/PR- lost significance in presence of the other negative factors and isolated ER-/PR- without any of the strong negative risk factors was not found.

Based on these validated (molecular) risk factors, an integrated risk assessment model was defined in which patients with p53-mutation, or >10% L1CAM or substantial LVSI were classified as *unfavourable* (~10%), and in the remaining patients those with *POLE*-mutation and without MSI or *CTNNB1*-mutation as *favourable* (~50%). Cases without those alterations were classified as intermediate. The integrated model significantly improved the area under the curve (AUC 0.73, 95%CI 0.66-0.79) compared to the model based on clinicopathologic factors alone (AUC based on original pathology reports 0.58, 95%CI 0.51-0.64 and based on central pathology review 0.63, 95%CI 0.56-0.69). When applying the integrated model to the PORTEC-1 and -2 patients confirmed to be high-intermediate risk after central pathology review (N=550), estimated 5-year rates of vaginal recurrence for favorable (N=274, 50%) vs. intermediate (N=195, 35%) vs. unfavorable (N=81, 15%) patients were 2.3% - 3.7% - 8.7% (p=0.091); locoregional recurrence 3.4% - 4.8% - 20.6%

(p<0.001); recurrence-free survival 94.4% - 91.4% - 65.5% (p<0.001), overall survival at 5 years 89.8% - 84.4% - 60.3%; see Stelloo *et al*, Clinical Cancer Research 2016[37].

In view of the above findings that the integrated molecular risk profile does provide meaningful insight in an individual patient's risk of recurrence and has been based on a similar group of patients as will be included in this study, is it now ready for prospective evaluation.

The first cohort of 50 patients shall be included in a pilot phase of the study, which will test the acceptability of this molecular-profile based treatment recommendation for eligible women and the logistics of this multicentre study in which the molecular profile has to be done and results given within 2 weeks from consent. If results are positive, the trial will continue (see trial design, sections 4 and 12).

3. Trial objectives

The primary objective of this study is to establish and compare the rates of vaginal relapse in patients with high-intermediate risk endometrial carcinoma treated with vaginal brachytherapy based on clinicopathological (standard) indications, compared with molecular risk profile-based recommendations for either vaginal brachytherapy, observation or external beam radiotherapy.

Secondary objectives are to establish and compare adverse events, patient-reported symptoms and health-related quality of life; pelvic and distant recurrence; 5-year vaginal control including treatment for relapse, recurrence-free and overall survival, and EC-related healthcare costs

4. Trial design

The first 50 patients shall be included in the pilot phase of the study. Primary objectives are to confirm the feasibility of logistics of this multicentre study, in which the molecular profile has to be done and results given within 2 weeks from consent, and the acceptability of this molecular-profile based treatment recommendation for eligible women. If results are positive, the trial will be continued.

In this multicenter phase III trial, 450 additional eligible women (for a total cohort of 500 evaluable women, including the 54 who were included in the previous PORTEC4 trial design with endometrioid type endometrial adenocarcinoma with high-intermediate risk features will be randomised (1:2) to one of the following arms:

1. Standard recommendation for vaginal brachytherapy (standard arm);
2. Molecular-profile based recommendation for observation (about 55%), vaginal brachytherapy (about 40%) or external beam radiotherapy (about 5%) (experimental arm)

See Appendix A for a summary figure of the trial design.

Primary study endpoint is vaginal recurrence. Stratification will be done by biased coin minimisation procedure for:

1. participating centre
2. grade (1 vs 2 vs 3)
3. type of surgery (lymphadenectomy yes/no)

5. Patient selection

5.1 Inclusion criteria

To be eligible for this trial, patients will need to meet all of the following inclusion criteria:

1. Histologically confirmed endometrioid type endometrial carcinoma, FIGO stage I, with one of the following combinations of stage, grade, age, and LVSI, or FIGO stage II (microscopic, grade 1):
    a. Stage IA (with invasion), grade 3 (any age, with or without LVSI)
    b. Stage IB, grade 1 or 2 and age ≥60 years
    c. Stage IB, grade 1 or 2 with documented LVSI
    d. Stage IB, grade 3 without LVSI
    e. Stage II (microscopic), grade 1.
2. Surgery consisted of Total Abdominal or Laparoscopic Hysterectomy and Bilateral Salpingo-Oophorectomy (TH-BSO). Pelvic lymphadenectomy is not recommended; however, if this has been done the patient is still eligible.
3. WHO-performance status 0-2
4. Written informed consent

5.2 Exclusion criteria

The following criteria exclude the patient from enrolment in this trial:

1. Any other stage of endometrial carcinoma
2. Non-endometrioid endometrial carcinoma, such as serous or clear cell carcinoma (in mixed types, at least 10% of serous or clear cell component), or undifferentiated carcinoma or carcinosarcoma or neuro-endocrine carcinoma.
3. Uterine sarcoma
4. Previous malignancy (except for non-melanomatous skin cancer) < 5 yrs
5. Previous pelvic radiotherapy
6. Interval between the operation and start of radiotherapy exceeding 8 weeks

6. Summary of treatment schedule (see also Appendix A)

Patients in the standard arm will be treated with vaginal brachytherapy (21 Gy HDR in 3 fractions of 7 Gy each, specified at 5 mm from the applicator surface and top, within overall time of 2 weeks).
Patients in the experimental arm will be either observed after surgery (55%) and followed closely for vaginal recurrence, or will receive vaginal brachytherapy as above (40%). The 5% who will be recommended pelvic external beam radiotherapy will received a dose of 45-48.6 Gy in 1.8-2 Gy fractions according to the centre's policy and technique. Vaginal toxicity will be evaluated before treatment (baseline), at completion of brachytherapy, an at 6 month intervals from randomization during the first 3 years, and annually thereafter. Quality of life and health-care costs will be evaluated at the same time points.
A log should be kept at each participating center of eligible patients, number of patients not entering the trial (with reason) and number included.

7. Staging and Treatment

7.1 Staging

Pre-randomisation evaluation procedures (see also the checklist in Appendix J):

1. Medical history, physical and complete pelvic examination
2. Baseline evaluation of vaginal atrophy and symptoms

3. Baseline quality of life evaluation

After surgery and pathology, the FIGO stage should be assigned on the basis of the surgical and histological findings (Appendix B).

7.2 Surgery

The surgical procedure could be done either by laparotomy, or by a laparoscopic approach. Laparoscopic procedures (laparoscopically assisted vaginal hysterectomy or total laparoscopic hysterectomy) are only permitted if the centre uses these as routine procedure (after completion of a learning curve). Thorough laparoscopic inspection of the abdominal content should be done, and a laparoscopic procedure should be converted to an open procedure if extra-uterine spread or metastases are identified or suspected.

The laparotomy procedure should start with an exploration of the intra-abdominal contents. The omentum, liver, peritoneal cul-de-sac and adnexal surfaces should be examined for possible metastases, followed by palpation for suspicious or enlarged nodes in the aortic and pelvic nodal areas. The uterus should be thoroughly evaluated for any breach in the serosa.

The standard surgical procedure is extrafascial total hysterectomy with bilateral salpingo-oophorectomy (TH-BSO) and histological verification of any suspected nodes or lesions. Pelvic and/or para-aortic lymph node sampling should be done in case of suspicious pelvic and/or para-aortic nodes.

7.3 Vaginal brachytherapy

7.3.1. Target Volume

The clinical target volume (CTV) consists of the proximal 4 cm of the vagina (including the paravaginal tissue containing the lymphatic vessels to a depth of 3 mm from the mucosal surface).

7.3.2. Technique and dose

High-dose-rate (HDR) brachytherapy should be given with a vaginal cylinder and should preferably be started between 4 and 6 weeks after surgery, and not before 3 weeks after surgery. PDR equipment may be used if the brachytherapy is given as HDR in fractions of 7 Gy (not in PDR schedule). At the first session, vaginal inspection and pelvic examination should be performed to confirm that the vaginal cuff has healed prior to therapy. Careful evaluation of the baseline vaginal width and length (as measured from the urethral ostium to the vault, using a transparent measuring cylinder set provided for this study) should be done, and baseline vaginal atrophy should be recorded. Care should be taken to obtain optimal contact of the cylinder to the vaginal apex mucosa, and the largest diameter cylinder (preferably 3.5 cm) should be chosen that fits tightly in the vaginal vault. The cylinder should be placed in the horizontal position (parallel to the treatment table, rather than pitching anteriorly or posteriorly).

Three fractions of 7 Gy, respectively, should be delivered, within an overall time of 2 weeks. The interval between the fractions should be at least 3 and maximal 7 days.

The prescribed dose is specified at the 100% isodose at 5 mm from the cylinder surface (point A2 in Appendix E, in which a typical loading pattern for a vaginal cylinder is shown). The loading pattern of the cylinder is symmetrical in the cranial-caudal direction, and chosen in such a way that the 100% isodose runs parallel to the cylinder surface at 5 mm distance. To account for the anisotropy in the longitudinal direction of the ^{192}Ir source, two points are defined at 5 mm from the top of the applicator (one along the central axis and the second 5 mm laterally from this point, see points A1 and A3 in Figure 1 in Appendix E). The average dose in these two points should be approximately 100%, while maintaining A1 ≥90% and A3 ≤110%. The most caudal

active dwell position is placed 3-3.5 cm from the first dwell position in the top of the cylinder, resulting in a 100% isodose length outside the applicator of approximately 4 cm from the top of the cylinder.
At (either before or after) the first brachytherapy session, a CT or MRI scan should be made that includes the applicator from the vulvar region to the top and extending at least 3 cm cranially from the apex of the cylinder. The proximal 3.5 cm of the vagina (as measured from the top of the cylinder) up to 3 mm from the cylinder surface should be contoured as CTV, and organs at risk (OAR), specifically the bladder, rectum, sigmoid and small bowel should be delineated up to a distance of at least 2 cm cranially from the cylinder. A standard treatment plan should be used for the first fraction, and dose distributions for the CTV and OAR should be recorded, and the 2cc doses in the OAR should be calculated for documentation and evaluation purposes. If at CT scanning the bladder, rectum or small bowel is located within 3 mm from the cylinder surface leading to a D2cc for bladder >7.5 Gy, rectum >7 Gy or small bowel >7 Gy per fraction, it is acceptable to slightly adjust the loading pattern to keep to these constraints for the next 2 fractions.
It is important to check the cylinder position and especially its contact with the vaginal apex mucosa by applying light pressure to the applicator just before and after CT/ MRI scanning and just prior to starting each HDR treatment. As no catheter is used, no specific bladder filling instruction is given, other than not voiding within 1 h before the procedure is started; thus it is expected that the bladder will be moderately filled during each treatment.

7.3.3. Quality Assurance

A dummy run procedure for vaginal brachytherapy will be performed for each centre prior to activation and first patient inclusion to ensure appropriate target coverage and dose, and to obtain equal treatment techniques for all study patients. Catheter reconstruction, contouring of CTV and organs at risk and brachytherapy planning and dose distribution will be evaluated.
During the course of the trial, QA of the brachytherapy will be performed by evaluating the brachytherapy plan of a trial patient for each centre once every second year.

7.4 External beam radiotherapy and treatment for vaginal recurrence

7.4.1 External beam radiotherapy

For the approximately 5% of patients in the experimental arm who will be receiving pelvic external beam RT, a dose of 45-48.6 Gy in 1.8-2 Gy fractions will be given according to the centre's policy and technique. CT planning will be used and individual target volume contouring for all patients, preferably with intensity-modulated radiotherapy (IMRT or volumetric arc therapy) if standard for the centre and with appropriate QA. In case of IMRT, CT planning scans in treatment position with (comfortably) full and empty bladder should be obtained and merged to obtain an internal target volume (ITV) accounting for movement of the vaginal vault region. The full bladder scan should be used for treatment planning, with dose specification at the isocenter and homogeneity requirements according to ICRU-83.

7.4.2 Treatment for vaginal recurrence

Patients with an observation policy who are diagnosed with vaginal recurrence during follow-up (without distant metastases) will be treated promptly with pelvic external beam RT to a dose of 45-48.6 Gy in 1.8-2 Gy fractions according to the centre's policy and technique, preferably with intensity-modulated radiotherapy if standard for the centre and with appropriate QA and technique as described in 7.4.1. This is followed by a

brachytherapy boost (3 x 6-7 Gy HDR, CT or preferably with MRI-based planning), aiming at a total dose of 80 Gy EQD2 dose (with α/β=10) in 90% of the tumor volume. Usually tumor regression is sufficient to be treated with intracavitary brachytherapy using a standard (or multichannel) cylinder or ovoids. In case of a thick vault recurrence with insufficient regression after EBRT for which the dose distribution from a cylinder or ovoids would not be appropriate, use of an interstitial technique (according to GEC-ESTRO guidelines) is permitted. If the recurrence is not considered suitable for EBRT plus VBT, surgery should be considered, followed by postsurgical EBRT and/or brachytherapy.

For MRI-based brachytherapy, the following constraints should be used: D2cc (EQD2 with α/β=3) for organs at risk: bladder < 80-85 Gy, rectum and sigmoid < 70-75 Gy, small bowel < 60-75 Gy. In case of pelvic or para-aortic lymph node recurrence (in absence of distant metastasis) the aim will be to deliver 60-66 Gy EQD2 with α/β=10 in the macroscopic involved lymph nodes, while treating the pelvic lymph node regions including one lymph node echelon proximal to the involved nodes to an elective dose (46 – 48.6 Gy).

8. Pathology

8.1. Histopathologic evaluation

The diagnosis of the regional pathologist will be first indication of eligibility for the trial. However, given the considerable number of discordances, with 8% discrepancies altering patient management[46], the specimens are centrally reviewed in Leiden during the pilot phase of 50 patients, and should after the pilot phase be reviewed by the reference pathologist at a regional gynaecologic oncology centre for which the lab has been validated for doing the molecular profile testing. Immediately at the oncology board discussion, or at consultation of the gynaecologist with the radiation oncologist at which eligibility is considered, the pathologist should be requested to send the histopathologic slides and blocks and a copy of the pathology report for review to the central or regional reference pathologist (section 8.2). The reference pathologist will keep a log of reviews performed, and number and items of discordances with and without consequences for patient management, respectively.

A standardized evaluation of the specimens according to international criteria is important to obtain information on the pathologic prognostic factors. It should be documented at which parts of the uterus the samples are obtained. The following samples should be obtained in all cases: a representative sample of the deepest myometrial invasion at a plane perpendicular to the serosal surface; a transversal section through the lower uterine segment just proximal to the endocervix; a longitudinal section through the lower uterine segment and endocervix, sections through both cornuae; and representative sections of the tumor.

Macroscopic evaluation should include:

- size and aspect of the uterus and adnexa, status of the serosal surface
- location of the tumor in the uterus (uterine body vs. lower uterine segment)
- size of the tumor (maximal diameter and thickness)
- invasion to < 50% or ≥ 50% of the myometrial width
- minimal distance (in mm) between the tumor and the serosa at the point of the deepest myometrial invasion
- width of the uninvolved myometrium
- involvement of the lower uterine segment and of the endocervix
- involvement of the fallopian tubes
- involvement of the ovaries

- size and number of lymph nodes if removed at surgery
- involvement of the omentum and any other tissue or biopsy obtained at surgery

Microscopic evaluation should include:

- histologic classification according to the International Society of Gynecologic Pathologists (Appendix D). For mixed endometrioid and serous or clear cell cancers, the percentage of each component should be recorded. Histologic type is serous or clear cell, respectively, if the proportion of this component is at least 10% (see Appendix D)
- histologic grade according to the FIGO criteria (Appendix D)
- invasion to < 50% or ≥ 50% of the myometrial width
- minimal distance (in mm) between the tumor and the serosa at the point of the deepest myometrial invasion
- involvement of the lower uterine segment
- involvement of the endocervical glands and/or the cervical stroma
- presence or absence of lymph-vascular invasion (LVSI)
- involvement of the ovaries, lymph nodes, peritoneal fluid sample or other tissue biopsies (if present)

Definition of LVSI: morphological vital tumor emboli in endothelial lined lumina containing erythrocytes and/or lymphocytes outside the tumor mass. Lumina following the outer contour of tumor fragments are to be considered shrinkage artefacts. LVSI is a microscopic H&E diagnosis (no additional immunohistochemistry).

8.2. Tissue specimen collection and molecular profile

After inclusion of a patient in the trial and obtaining informed consent, the pathologist will be requested to send all histopathological slides and at least one representative paraffin-embedded sample of the tumor for pathology review and determination of the molecular profile.

For patients in the experimental arm, quantification of LVSI and determination of the molecular profile including POLE CTNNB1 mutation; L1-CAM, P53 and MMR protein expression (MLH1, PMS2, MSH2, MSH6),and ER/PR will be done promptly after receiving the tissue block at LUMC, and the results will be sent by fax or secure email within 7 working days of receipt of the block. Cut-offs for positivity of the immunohistochemical molecular markers will be used according to previous published methods.

The favourable group (about 55%) will include patients with POLE mutations, and others with microsatellite stable and CTNNB1wild type profile, without substantial LVSI - for these patients observation will be recommended.

The unfavourable group (about 5 %) will include those with p53-mutation or L1CAM positivity or substantial LVSI and based on their higher locoregional relapse risk and lower recurrence free survival pelvic external beam radiotherapy will be recommended.

All others will be designated intermediate (about 40%), and for these patients vaginal brachytherapy will be recommended. In case of technical failure of the molecular analysis and no high-risk factor, the patient will be designated intermediate risk and receive VBT as in the standard arm (expected: 1%). In case patients cannot be clearly assigned to a subgroup because of multiple alterations (expected: 2%), treatment group will be assigned as follows:

1. if POLE mutation: favourable (irrespective of any other factor)
2. if other classifier than POLE and substantial LVSI: unfavourable

3. if other classifier than POLE and L1CAM: unfavourable
4. if MMRd and p53 mutation: intermediate;
5. otherwise: based on the most unfavourable factor.

In case of loss of MMR-protein expression this is most often based on MLH1-promoter hypermethylation. However, if no methylation is found, the patient (in both arms) will be contacted as she should be informed about this and be referred to a clinical geneticist to rule out Lynch syndrome. This is expected to be found in 3-5% of all cases.[38]

The tumour blocks of the patients in the standard arm will be saved in a dedicated tissue bank for determination of the molecular risk profile for detection of possible Lynch syndrome within 8 weeks, and for full comparison at a later stage. Remaining tissue of the tumour block of patients in both arms will be stored in the tissue bank and used for further translational work to find new molecular risk factors and targets; all other blocks and slides will be returned to the local pathology lab.

Pathology review and determination of the molecular profile will during the pilot phase of the trial be done in one single gynaecologic pathology centre (LUMC). During the pilot phase, additional expert gynecologic pathology centres who have the technical facilities and expertise and wish to determine the profile, will be validated for the trial. The aim is to have 4 pathology centres in the Netherlands doing review and determination of the profile after the pilot phase has been completed.

9. Follow-up, toxicity evaluation and adverse events

9.1. Follow-up

At the completion of brachytherapy or EBRT, an end-of-treatment follow up visit after 3-4 weeks should be planned by the radiation oncologist. At this visit, adverse events and acute vaginal toxicity will be assessed. Patient education on sexual issues and coaching on resuming sexual activities and/or potential use of vaginal dilators, if appropriate, should also be done at this visit. The importance of pelvic floor exercises (especially in case of minor incontinence) may be discussed. The Quality of life Questionnaires will be sent directly to the patients' home address (provided permission has been given, see section 11).

Patients will be evaluated during alternating follow-up visits to their gynecologist and radiation oncologist every 3 months for the first 3 years, and at 6 month intervals thereafter. At each of these FU visits a specific history will be obtained and pelvic examination will be done. Routine vaginal vault cytology is not indicated; however, prompt evaluation with biopsy should be done in case of any suspicious vaginal lesion. CT- or MRI scans are to be obtained in case of pelvic or abdominal symptoms or signs of recurrence.

Due to the alternating FU visits, patients will be assessed by their radiation oncologist every 6 months for the first 3 years, and every 12 months up to 5 years. At these visits to the radiation oncologist, specific assessment of adverse events and vaginal effects will be done. EC-related healthcare use will be assessed at these time points as well. The QoL questionnaires will be sent to the patients at the same time intervals, plus at 7 years from the date of randomisation.

Long-term outcome evaluation at 7 and 10 years should be obtained, preferably by follow-up visits, or by telephone, or at least by General Practitioner enquiry.

Follow-up CRF are required at 6-month intervals from the date of randomization during the first 3 years, annually in the 4th and 5th year; at year 7 and 10 and at each trial event (see Appendix I and H).

9.2. Reasons for going off treatment

If a patient is going off protocol treatment, the reason should be documented on the CRF according to the following listing:

- normal treatment completion
- progressive disease
- adverse event
- intercurrent disease / events
- refusal or other reasons

All patients will remain in follow-up for outcome information and quality of life and health care costs, unless they have withdrawn informed consent for follow-up information. Quality of life will be stopped in case of distant metastases of a life-threatening other disease.

9.3. Adverse events and reporting of adverse events

9.3.1. Definitions

An **adverse event** (AE) is any symptom, sign, illness or experience, which develops or worsens in severity from informed consent to up to 30 days following the last administration of any of the study treatment. Intercurrent illnesses or injuries should be regarded as adverse events.
Adverse events are classified as either serious or non-serious.
A **serious adverse event** (SAE) is any adverse event that is:
- fatal
- life-threatening
- requires or prolongs hospitalisation
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event.

Important medical events are those which may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardise the patient, and may require intervention to prevent one of the other serious outcomes.

9.3.2. Adverse events (AE)

Special attention should be paid to the occurrence of adverse events (AE) throughout the study period. All observed toxicities should be graded according to the NCI-Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.0, Appendix F) and documented on the Toxicity Form (Form 6).
The clinical course of each event should be followed until resolution, stabilisation or until it has been determined that study treatment or participation is not the cause.

9.3.3. Serious Adverse Events (SAE)

Although SAE due to the study treatment are expected to be rare, all standard procedures for SAE reporting will apply. All SAE occurring during the treatment period and within 30 days thereafter, whether or not considered to be related to the study treatment, must be reported **within 24 hours** by fax to the central data management office (Netherlands: IKW Trial Office, Leiden, fax +31 71 526 6712), using the completed SAE form, and thereafter documented in detail, as indicated on the SAE form. Information is required as to the date and time of onset, duration, AE-term and peak intensity (according to the NCI-CTCAE version 4.0), and

outcome of the adverse event (recovered completely; residual effects; continuing). The investigator should classify the relationship of a SAE to the treatment (none; unlikely; possible; probable; definite). The investigator must respond to queries and requests for additional information **within 24 h**.
LUMC, the Sponsor ("verrichter" in the terminology of Dutch law) is responsible for SAE assessment and reporting to the authorities in accordance with all requirements of the Dutch law. LUMC has delegated these responsibilities, especially the evaluation of expectedness, to the principal investigator of this study.
All SAE reports will be handled and assessed according to these legal requirements. Upon receipt of a SAE report at the IKW Trial Office at LUMC Leiden, the legal procedures for SAE registration will be followed. The principal investigator of the study will be promptly notified, and the causality of the SAE as not, unlikely, possibly, probably or definitely related to the study treatment will be recorded.
Any SAE occurring after the 30-day period, throughout follow-up, should be reported promptly if considered possibly, probably or definitely related to the protocol treatment.

9.3.4. Summary of procedures for reporting of SAE:

- Local investigator to send first SAE report **< 24 h** to IKW Trial Office at LUMC (fax +31 71 526 6712)
- Additional SAE information with comments to be sent **< 1 wk**

- **SUSAR**: not applicable for this type of research not involving medicines
- **Annual safety reports:**
  - Bi-annual reports of all SAE will be sent to the DSMB, Central Ethics Committee, Dutch competent authorities, and local investigators

10. Registration, randomisation and data monitoring

10.1 Registration

Patients who are eligible for the study should be referred to the radiation oncologist immediately after the operation. Preferably, the gynecologist already mentions the trial and briefly explains its principles. The radiation oncologist further explains the rationale and design of the trial and the respective treatment procedures, and hands out the patient information. If informed consent is obtained, the radiation oncologist contacts the Data Center for registration and randomisation. The patient should be registered via internet. The information which will be requested at registration is summarised on the randomisation checklist, which should be filled in prior to registration. Each patient will be given a unique trial number. To ensure patient privacy, the patient will be registered by trial number and hospital-sequence code (hospital initials and sequence study number at the hospital), and these will be used for the database, follow-up information and correspondence. Date of birth will only be noted as item on the registration form, as age is an important prognostic factor in endometrial carcinoma. The pathology number will be asked to ensure receipt of the correct slides and tissue sample, however, the storage of samples will be done using study number only.

10.2. Randomisation

Central randomisation will be done via internet with stratification by participating centre, tumor grade and type of surgery, using a biased coin minimisation procedure. The trial number and result of randomisation will be obtained via the Internet randomization system and confirmed by email.

10.3. Data handling, monitoring and quality control

Central and local datamanagers will monitor the recruitment, the reported serious adverse events and the data quality at least every 2 months. Problems which are identified will be discussed with the principal investigators, who will take appropriate measures.
Relevant information will be discussed during the Annual Investigator's Meeting, and will be included in annual study reports to the Central Ethics Committee (CME) and the Data and Safety Monitoring Board (DSMB). 6-monthly SAE and Accrual Reports will be sent to local investigators, CME and DSMB.

Data handling, validation and data management will be conducted according to the Standard Operating Procedures (SOPs) of the central data management organization Integraal Kankercentrum Nederland (IKNL), which are compliant to Dutch and EU laws, the SOPs of DGOG and to those of the Gynecological Cancer Intergroup. At IKNL specific data management and data validation plans for the PORTEC-4a trial are in place, based on these SOPs.

Central and on-site monitoring

Central monitoring will be done at least every 6 months and will include evaluation of data timeliness, data integrity, completeness of all data entered in the TRIAS system via eCRF and any other checks that have been described in the data management and data validation plans.

As the study has a negligible-risk profile, on-site monitoring will be limited.
On-site monitoring will be done by designated monitors, at least once in each centre, but in principle once every 2 years (and annually if needed on the basis of the previous visit).
The aim of on-site visits will be:

- To assess the consistency of the data reported on the CRF with the source data (source data verification)
- To check that all SAEs have been properly reported

11. Quality of life assessment

For the evaluation of the general quality of life the EORTC (European Organisation for Research and Treatment of Cancer) Core questionnaire (QLQ-C30 version 3.0) will be used (Appendix G). The EORTC QLQ-C30 is a multidimensional, cancer-specific quality of life questionnaire developed by the EORTC Study Group on Quality of Life (QOL) for repeated assessments within clinical trials. It is developed in a cross-cultural setting and has been found valid and reliable for quality of life assessments in various cancer populations, irrespective of the specific diagnosis. Optional modules developed for specific diagnostic groups or specific treatment modalities can supplement it. The QLQ-C30 contains five functional scales (physical, cognitive, emotional, social and role functioning), a global health status/quality of life scale, three symptom scales (pain, fatigue and nausea/vomiting), and six single items assessing additional symptoms (dyspnoea, insomnia, loss of appetite, constipation, diarrhoea) and perceived financial impact. For the majority of the QLQ-C30 items a 4-point Likert-type response scale is used. Exceptions are the items for the global quality of life scale (were a 7-point scale is used). All subscale and individual item responses are linearly converted to 0 to 100 scales. A higher score for a functional and global quality of life scales represents a better level of functioning. For the symptom scales and items, a higher score reflects a higher level of symptoms and decreased quality of life.
In addition to the QLQ C-30 core questionnaire, the EORTC module for endometrial cancer EN24 will be used, and some additional questions regarding vaginal symptoms, sexual symptoms and distress. See Appendix G.

During the informed consent procedure, the radiation oncologist hands over the baseline QoL questionnaire and a pre-stamped return envelope. The patient receives a separate consent form on which she is asked to fill out her name and address to be kept in a separate data file for the sole purpose of enabling the Data Center to send the subsequent QOL questionnaires to her home address. If the patient declines, the QoL questionnaire collection is left to the responsibility of the local investigator, however, in practice patients readily consent as they consider the quality of life assessments valuable.
After receiving the baseline questionnaire and address sheet at the Data Center, the patient's name and address information will be entered in a separate database, which will exclusively be used for sending out QoL questionnaires.
QoL questionnaires will be handed out by the radiation oncologist at baseline. From then on, the QOL questionnaires will be sent directly to the patient's home address at completion of brachytherapy (or at 6 weeks after randomisation for patients who had observation in the molecular arm) and at 6, 12, 18, 24, 36 and 60 months and at 7 years from the date of randomisation.

12. Statistical considerations

12.1 Number of patients and power calculation

Based on incidence rates provided by the Dutch Cancer Registry (over 1900 new cases per year), the theoretical number of patients in The Netherlands who may be eligible for the trial is about 450 per year, as the subgroup with high-intermediate risk factors constitutes about 30% of all EC patients and some will be too old or frail. Assuming a realistic 35% accrual rate to the study, and participation by 85% of the centers, the calculations have been based on an accrual rate of 130 patients per year in the Netherlands.
The study is based on a recruitment period of 4 years after amendment, and a follow-up duration of 36 months after inclusion of the last patient before definite analysis. It is expected that the yearly accrual rate in the Netherlands will be 100-130 patients. Thus, a total of 450 patients may be accrued in a 4-year period
The minimum target number of patients for this new trial design is 450 evaluable patients (50 in the pilot phase and 400 after completing the pilot), for a total of 500 evaluable patients, as the patients (n=54) who were included during the previous trial design will be added to the standard arm if they had VBT (two-thirds of these patients), and those who had observation (one-third) will be added to the experimental arm if their molecular analysis profile shows a favourable profile. Cases with technical failure of the molecular analysis (expected <1%) and those with early informed consent withdrawal will be accounted for by extra inclusion to obtain 500 evaluable patients in the trial.
International collaboration will be sought to ensure rapid and timely completion of recruitment; if in the first 2 years after other groups have been activated the rate of recruitment would be significantly more than 100 patients per year, the target number may be increased by a protocol amendment to increase discriminative power between the outcomes of the molecular subgroups.

The design of the trial is a non-inferiority study, based on the primary endpoint of 5-yr cumulative incidence of vaginal recurrence (VR). VR is defined as all vaginal recurrences as first failure, including simultaneous occurrence of pelvic (PR) or distant recurrence (DR) together with a vaginal recurrence. Other recurrences (regional and distant) and death are considered competing risks.
Based on data from PORTEC-2 trial and the molecular analysis from the pooled PORTEC-1 and 2 trials, the expected 5-year rates of VR will be:

- 2.0% in the vaginal brachytherapy (VBT) arm
- 4.625% in the experimental molecular analysis arm (based on 55% favourable patients with 7% VR rate after observation; 40% intermediate patients with 1.5% VR rate after VBT and 5% unfavourable patients with 3.5% VR rate after EBRT).

Assumptions are: for VR constant cause-specific hazard rates (per year) of 0.0044 over the first 5 years in the VBT arm and 0.0104 in the molecular arm, and for the competing risk a constant cause-specific hazard rate (per year, over the whole follow-up period) of 0.0353 and 0.0358 in the VBT and molecular arms, respectively. These assumptions coincide with a 5-yr cumulative incidence of VR of 2% in the VBT arm and 4.625% in the molecular arm and a 5-yr cumulative incidence of competing risk of 16% in both arms. Further assumptions are uniform accrual of patients in 4 years with 3 additional years of follow-up, and no loss to follow-up. The null hypothesis states that the 5-yr cumulative incidence of VR in the molecular exceeds that of the VBT arm by more than an equivalence margin of 7%; the alternative hypothesis is that the 5-yr cumulative incidence of VR in the molecular may exceed that of the VBT arm by no more than the equivalence margin of 7%. The test to be performed is based on the estimated (non-parametric) 5-yr cumulative incidences of VR in both arms, along with associated standard errors. The difference in 5-yr cumulative incidences of VR between the arms can be calculated from these, with variance equal to the sum of the variances of the estimates in the separate arms. The null hypothesis will be rejected if the upper bound of the one-sided 95% Wald confidence interval of the difference (molecular minus standard) does not exceed the equivalence margin. For a total of 500 evaluable patients, with 167 patients in the standard arm and 334 in the molecular arm, a power of 84.4% is achieved (based on 10.000 simulations). The estimated power with these numbers of patients is 89.7% for an equivalence margin of 7.5%, and 94.1% for an equivalence margin of 8%.

In both study arms there will be patients receiving vaginal brachytherapy (about 40% in the experimental arm, 100% in the standard arm). A second power calculation was done, again based on a non-inferiority approach, where the comparison is between the favourable patients in the standard arm (receiving VBT) and the favourable patients in the molecular arm (who receive observation). Again accounting for the same competing risks we assume for VR constant yearly cause-specific rates over the first 5 years, and for the competing risks a constant cause-specific hazard rate (per year, over the whole follow-up period). These constant rates were chosen so that the 5-yr cumulative incidence of VR equals 1.5% in the standard arm and that the 5-yr cumulative incidence of the competing risks in the favourable group equals 12% in both arms. Further assumptions are, as before, uniform accrual of patients in 4 years with 3 additional years of follow-up, and no loss to follow-up. Based on the same statistical principles as above, the table below shows the estimated power for non-inferiority tests with an equivalence margin of 8.5% for given 5-yr cumulative incidences of VR in the favourable subgroup of the molecular arm, along with the standard error of the difference.

5-yr cumulative incidence of VR				
Standard arm	Molecular arm	Equivalence Margin	Power	SE difference
1.5%	1.5%	8.5%	100%	0.0154
1.5%	3%	8.5%	97.8%	0.0183
1.5%	4%	8.5%	89.7%	0.0199
1.5%	5%	8.5%	75.4%	0.0213

1.5%	6%	8.5%	56.2%	0.0226
1.5%	7%	8.5%	37.6%	0.0238

In view of the limited power of the non-inferiority approach with an expected difference in VR between the groups, the comparison of the VR rate will largely be descriptive, with the aim to estimate the difference in VR with sufficient precision (standard error of the difference below 2.4%).

12.2 Stopping rule, safety reviews and interim analyses

An Independent Data and Safety Monitoring Board (DSMB), consisting of at least two clinicians (a radiation oncologist and a medical oncologist experienced in clinical trials and not entering patients into the trial), and an independent statistician will be appointed to monitor the study.

Death and failure rates and SAE reports for both treatment arms will be closely monitored in order to pick up any (unexpected) trends. Safety reviews will be presented confidentially to the DSMB every year, and/or at request of the DSMB. These annual reviews will include data on SAEs, number and causality of deaths, number of recurrences and serious adverse events. Only if the DSMB recommends that the study should be stopped or modified, the results will be made public to the principal investigators.

After inclusion of the pilot phase a descriptive analysis will be performed of the logistics and patient acceptability of the study, and a general report (not split by arm) of the number of deaths, events and recurrences will be presented to the DSMB. After this point, an annual confidential report will be generated and presented to the DSMB. This report includes by treatment arm the number of entered and at that time evaluable patients; treatment given; the number of deaths and causes of death; number of failures and types of failure, and in case of VR the subsequent treatment results; and incidence, types and grades of adverse events. The DSMB is free in its public recommendations to the Study Coordinators and confidential recommendations to the study statistician. Only if the DSMB recommends that the study should be stopped or modified, the results will be made public.

12.3 Statistical analysis

All analyses concerning treatment effects will be done according to the intention-to-treat principle. The primary endpoints for the comparison of the two treatment arms is vaginal recurrence; second primary endpoint is recurrence-free survival. Secondary endpoints are adverse events, patient-reported symptoms and quality of life, pelvic and distant recurrence, 5-year vaginal control including treatment for relapse, overall survival, and EC-related healthcare costs.

Formal tests for the differences in relapse and survival rates between the two arms will be done with the Kaplan-Meier method, the log-rank test and Cox regression analysis. The incidence of late vaginal effects will be analyzed actuarially with the Kaplan-Meier method, the log-rank test and Cox regression analysis.

Multivariate analysis of prognostic factors, especially stage, histological grade, and lymph-vascular space invasion will be done using logistic and Cox regression analyses.

Time-to-event analyses will be performed using log-rank tests with date of randomization as starting point. The competing risk method will be used, with competing risks of death, PR and DR for analysis of VR, and competing risk of death for analyses of PR and DR. Kaplan-Meier method will be used for OS and DFS. A first failure competing risks analysis will be performed where the first failure type is distant if there are DM, with or

without simultaneous VR or PR; the failure type is PR in case of PR with or without VR; the first failure type is VR in the case of isolated vaginal recurrence.

Analysis of toxicity will be based on treatment received. Patient- and tumour characteristics and toxicity data will be compared using chi-square statistics or Fisher's exact test for categorical variables, and *t* test for continuous variables; a p-value < 0.05 will be considered statistically significant.

EC-related healthcare costs will include the costs of the randomised care and care associated with (serious) adverse events. Healthcare use over the follow-up period will be converted to costs using standard prices, discounted over time. Costs will be compared according to the intention-to-treat principle, using *t* tests with multiple imputation to account for missing data.

12.4 Statistical analysis of the quality of life assessment

All patients with a valid baseline and at least one follow-up QOL questionnaire will be included in the analysis. The baseline questionnaire is considered valid if filled out and dated by the patient before the starting date of trial treatment. Reasons for missing baseline and follow-up questionnaires will be assessed. To evaluate the differences between the treatment groups with respect to the effect of treatment burden on life-quality during and up to 5 years after treatment, the repeated measures of the QLQ-C30 and EN24 functional and symptom scales and of the global health index will be analysed using mixed ANOVA models. The single items in the QLQ-C30 and EN24 will be analysed using (ordinal) logistic regression with random effects. Missing data of patients dropping out of the study will be handled as missing-at-random; the appropriateness of this assumption will be assessed by fitting a joint model to survival and QOL-data or by fitting pattern-mixture models. The items concerning the diagnosis-specific symptoms will be summarized using the unweighed sumscore. The reliability and validity of this sumscore will be established using baseline data, and -when sufficient- the effect of treatment on this sumscore will be evaluated using mixed ANOVA models.

13. Ethics

The study protocol and any amendment that is not solely of an administrative nature will be submitted for approval by the Institutional Ethics Committee (METC). In the law (Wet medisch-wetenschappelijk onderzoek met mensen, WMO) rules for the scientific and ethical review of trials involving human subjects have been formulated. The guidelines "richtlijn toetsingsprocedure multicenter-onderzoek" (active as of January 1, 2001) and "good clinical practice" will be applicable. The protocol will be submitted for review to the LUMC Medisch-Ethische Toetsings Commissie (Commissie Medische Ethiek, CME), which will contact the Board of Directors of the participating centers for statements of local consent.

The study will be conducted in full conformance with the ethical principles of the Declaration of Helsinki and the WMO.

The rationale, design and aims of the study will be explained to each patient along with the specific information on the respective treatment arms. The principles of randomisation and registration and the follow-up procedure will be clarified. The patient will receive written patient information (see Appendix G) and will have ample opportunity to ask questions. The patient will have sufficient time to consider the study before deciding to participate. Written informed consent of the patient is required before randomisation. This consent will include registration in the trial, data processing and sending diagnostic material for pathology review.

An Independent Data and Safety Monitoring Board (DSMB) will be appointed to supervise the trial, ensure its conduct is according to GCP, and to provide advice to the study coordinators on continuing or stopping the trial, or modifying the protocol (see section 12.2)

14. Trial insurance

According to the law (WMO), every participating institute should have an insurance against the legal liability resulting from medical procedures. In addition, specific trial insurance will be organized by each participating center and/or each participating group as determined by ethical and legal regulations. Patients will receive written information on the trial insurance for this study.

15. Publication policy

The final publication of the trial results will be written by the study coordinators on the basis of the statistical analyses performed by the trial statistician. A draft manuscript will be submitted to all co-authors for review. After revision by the co-authors, the manuscript will be sent to a peer-reviewed scientific journal. Authors will include the central study coordinators, the PIs of all participating groups, investigators from the participating centres who have included more than 8% of the evaluable patients in the trial (by order of inclusion), the statistician, the lead review pathologist, and others who have made significant scientific contributions. PIs of a single participating site of their country will be included as author if either (1) their site included at least 6% of the evaluable patients in the trial and/or (2) if their site made a significant contribution to the trial. A listing of all participating investigators will be included in an appendix to the publications. Publications regarding specific sub-analyses or side studies (e.g. pathology) will be written by the respective lead investigators, in cooperation with the study coordinators.

Any publication, abstract or presentation involving patients included in this trial must be approved by the study coordinators. Such a publication cannot include any comparisons between randomised treatment arms, nor an analysis of any of the study endpoints unless the final results of the trial have already been published. Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses, but no comparisons between randomised treatment arms may be made public before the recruitment is discontinued.

16. List of participating groups, centres and local investigators

16.1. The Netherlands – DGOG (in alphabetical order) and expected annual recruitment

1.	Academic Medical Center, Amsterdam (G.H. Westerveld)	5
2.	Catharina Hospital, Eindhoven (H. van den Berg)	8
3.	Erasmus Medical Center, Rotterdam (J.W. Mens)	10
4.	Institute Verbeeten, Tilburg (K. De Winter)	10
5.	Isala Clinics, Zwolle (L. Zwanenburg)	5
6.	Leiden University Medical Center (R. Nout, C.L. Creutzberg)	10
7.	MAASTricht Radiation Oncology Clinic (L. Lutgens)	12
8.	Medical Centre Haaglanden-Bronovo, Den Haag (T.Stam)	5
9.	Medical Spectre Twente, Enschede (J. Peer-Valstar/E. Hendriksen)	12
10.	NKI/Antoni v. Leeuwenhoekhuis, Amsterdam (M. Bloemers)	10

11. Radiotherapy Group, Arnhem (E. van der Steen-Banasik)	10
12. Radiotherapy Group, Deventer (S. van de Pol)	8
13. Radiotherapy Institute Friesland, Leeuwarden (A. Slot)	8
14. University Medical Center Groningen (S. Bijmolt)	8
15. University Medical Center Radboud, Nijmegen (A. Snyers)	8
16. University Medical Center Utrecht (I. Jürgenliemk-Schulz)	12
17. Zuidwest Radiotherapy Institute (V. Coen)	5

16.2 Belgium - University Hospital Gent (K. Vandecasteele) – in set-up

16.3 Australia and New Zealand - ANZGOG group (pending funding)

16.4 Ireland - Irish Clinical Trials Group (in set-up)

16.5 France - GINECO group (pending funding)

16.6 Germany - University Hospital Tubingen (starting set-up)

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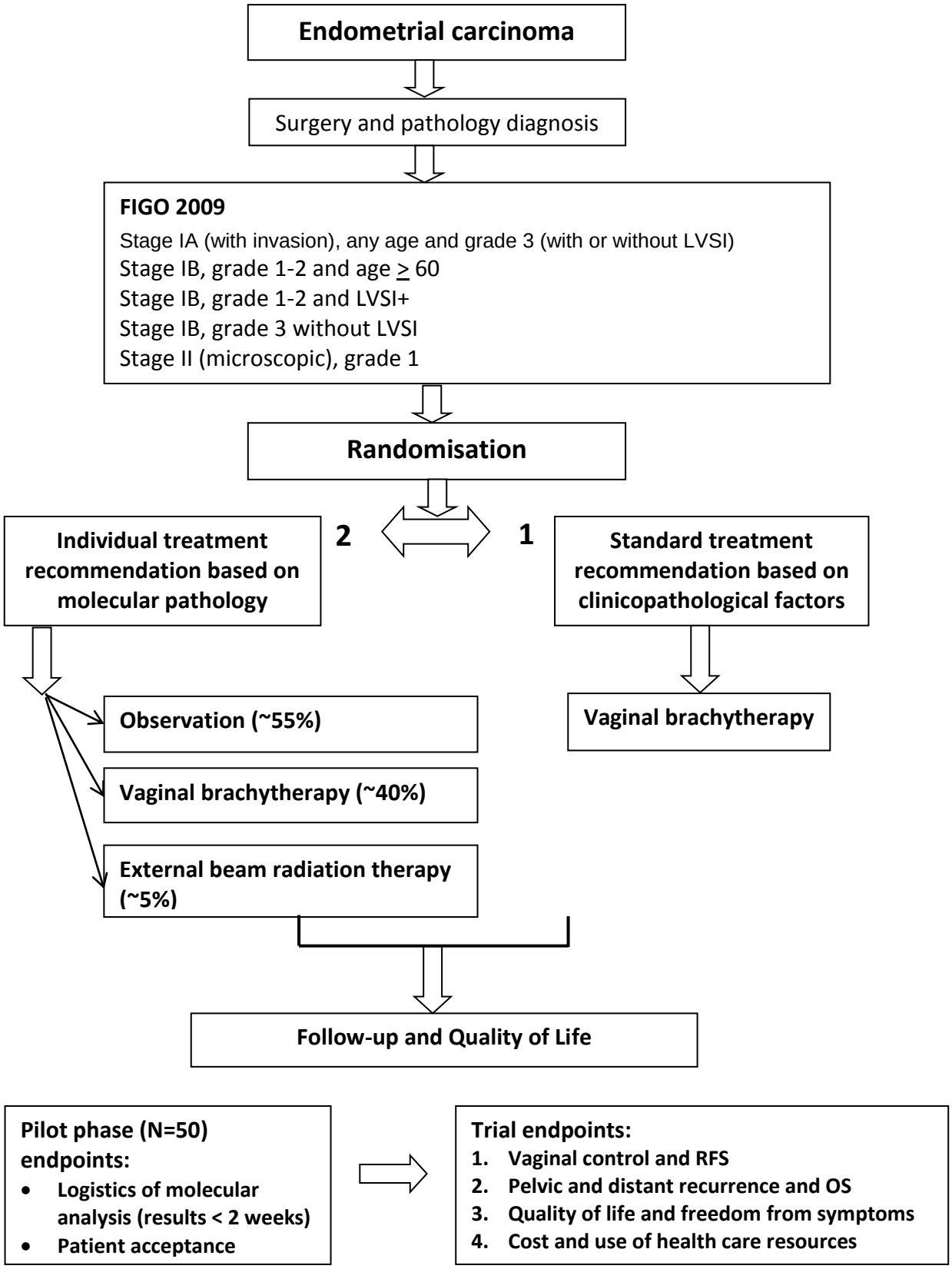
APPENDIX A. SUMMARY PORTEC-4 (Design amended PORTEC-4 trial v.2.0)



APPENDIX B. FIGO STAGING

FIGO 2009 staging for carcinoma of the endometrium

Stage I*	**Tumor confined to the corpus uteri**
stage IA*	No or less than half myometrial invasion
stage IB*	More than half myometrial invasion
Stage II*	**Tumor invades cervical stroma, but does not extend beyond the uterus****
Stage III*	**Local and/or regional spread of the tumor**
stage IIIA*	Tumor invades the serosa of the corpus uteri and/or adnexae[#]
stage IIIB*	Vaginal and/or parametrial involvement[#]
stage IIIC*	Metastasis to pelvic and/or para-aortic lymph nodes[#]
IIIC1*	Positive pelvic lymph nodes
IIIC2*	Positive para-aortic lymph nodes with or without pelvic nodes
Stage IV*	**Tumor invades bladder and/or bowel mucosa, and/or distant metastasis**
stage IVA*	Tumor invasion of bladder and/or bowel mucosa
stage IVB*	Distant metastasis, including intra-abdominal metastases and/or inguinal lymph nodes

* Either G1, G2 or G3 (G is FIGO grade)

** Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II

[#] Positive cytology has to be reported separately, without changing the stage.

APPENDIX C. PERFORMANCE STATUS (WHO-ECOG)

Grade 0	Fully active, able to carry out all normal (pre-disease) activity without restriction
Grade 1	Restricted in physically strenuous activity but ambulatory and able to carry out light work, e.g., light house work, office work
Grade 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Grade 3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
Grade 4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

APPENDIX D. HISTOLOGIC CLASSIFICATION AND GRADING SYSTEM

International Society of Gynecologic Pathologists Classification for Endometrial Carcinomas

1. Endometrioid adenocarcinoma
2. Mucinous carcinoma
3. Serous carcinoma
4. Clear-cell carcinoma
5. Squamous carcinoma
6. Undifferentiated carcinoma
7. Mixed types
8. Miscellaneous carcinoma
9. Metastatic carcinoma

Histologic classification of mixed carcinomas:
Mixed serous and endometrioïd carcinomas and mixed clear cell and endometrioid carcinomas should be classified as serous or clear cell carcinomas if they contain at least 10% of a serous or clear cell component, respectively, and otherwise be classified as endometrioid.

International Federation of Gynecology and Obstetrics (FIGO) and Armed Forces Institute of Pathology (AFIP) histologic grading system

G1 tumors have 5% or less of a nonsquamous or nonmorular solid growth pattern

G2 tumors have 6% to 50% of a nonsquamous or nonmorular solid growth pattern

G3 tumors have more than 50% of a nonsquamous or nonmorular solid growth pattern

A higher degree of nuclear atypia (in comparison with the architectural grade) raises the grade of a G1 or G2 tumor by 1.

Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

APPENDIX E. VAGINAL BRACHYTHERAPY

Figure 1 below shows a coronal schematic view of a standard vaginal cylindrical applicator, 35 mm in diameter, and 35 mm length of activated source positions.
All applicator points A are at 5 mm distance from the surface of the applicator.
Applicator points A1 and A3 are located 5 mm cranially from the applicator, with point A1 at the central axis of the applicator (in the "dip" of the dose distribution, due to anisotrophy) and point A3 5 mm laterally from A1 (in the "shoulder" of the dose distribution).
Applicator points A2, A4, A5 and A6 are all parallel to the central axis at 5 mm from the cylinder surface. The prescription point A2 is positioned halfway the length of activated source positions (starting from the 1st source position, even if this position is not activated), and receives 100% dose by definition. A5 and A6 are placed at 1 cm cranially and caudally to A2. For the points A5 and A6 the aim is to reach 95-100% of the prescribed dose, and not to exceed 100%. A4 is positioned at the level of the first possible source position at 5 mm from the surface, and will receive a lower dose as the isodose follows the curvature of the cylinder surface. Depending on the anisotropy of the source used, point A1 can receive a (5-10%) lower dose than the prescribed dose and point A3 a (5-10%) higher dose. The mean dose to points A1 and A3 should be 100%, while maintaining A1 ≥90% and A3 ≤110%. The most caudal active dwell position is placed about 3.0-3.5 cm from the top of the cylinder, resulting in the 100% isodose running parallel at 5 mm from the surface, tapering caudally and entering the cylinder at approximately 4 cm from the top of the cylinder.
In Figure 2 on the next page, typical dose distributions are shown for cylinders of 35 and 30 mm width.

Figure 1.

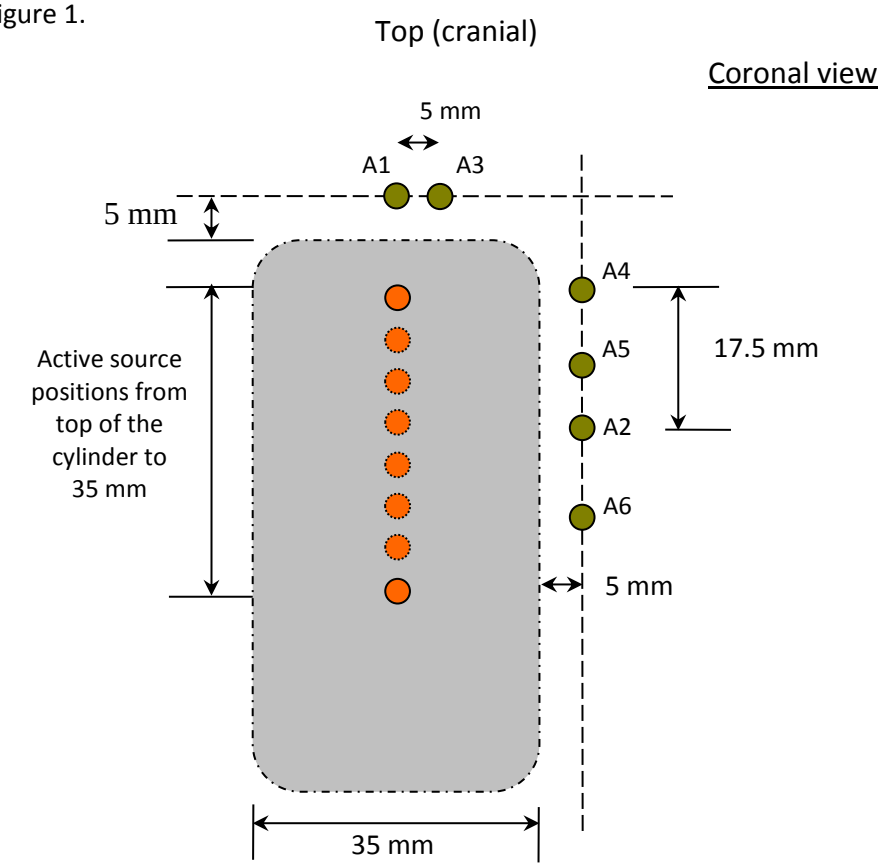
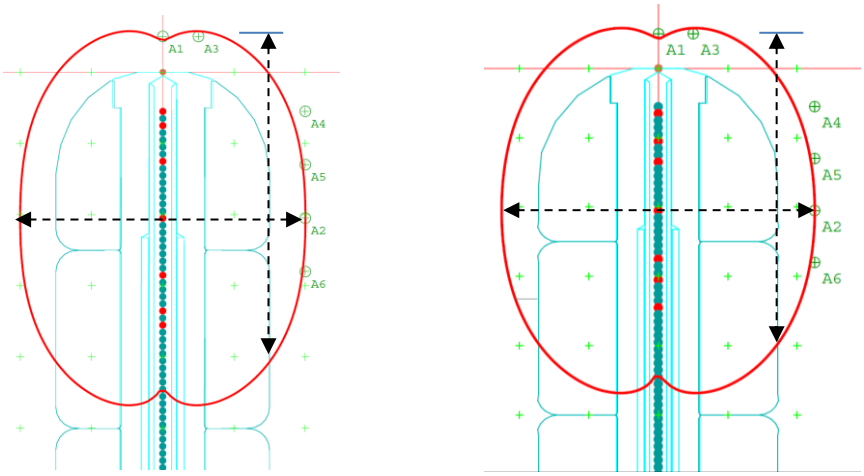


Figure 2.



Dose distributions for vaginal cylinders of 30 mm (left) and 35 mm width (right). The loading pattern of the cylinder is symmetrical in the cranial-caudal direction, and chosen in such a way that the 100% isodose runs more or less parallel to the cylinder surface at 5 mm distance.
The isodose line depicts the 100% isodose (red).

Compare the reference points to Figure 1 on previous page:
Prescription point A2
Cranial points A1 (at central axis) and A3 (5 mm laterally)
Applicator points A4, A5, A6

◄- - -► Reference Volume Width (max width of the 100% isodose in mm at the level of A2)

↕ Reference Volume Length (max length of the 100% isodose in mm from the top of the 100% isodose to the level where the 100% isodose enters the cylinder)

APPENDIX F. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 will be used for scoring of adverse events. The CTCAE v4.0 Document and other information can be downloaded from http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
The CTC website http://ctep.cancer.gov/ also includes conversion tables from CTCAE v3.0.

The adverse event (AE) grade refers to its severity. The CTCAE v4.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE, based on this general guideline:

Grade 1	Mild AE; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate AE; Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe AE; Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening or disabling AE; urgent intervention indicated
Grade 5	Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Common Terminology Criteria for Adverse Events v4.0 (CTCAE) - Excerpt for reference:

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Reproductive system and breast disorders				
CTCAE v4.0 Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Vaginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-
Vaginal fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; intervention indicated
Vaginal hemorrhage	Minimal bleeding identified on clinical exam or imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; operative intervention indicated
Vaginal inflammation	Mild discomfort or pain, edema, or redness	Moderate discomfort or pain, edema, or redness; limiting instrumental ADL	Severe discomfort or pain, edema, or redness; limiting self care ADL; small areas of mucosal ulceration	Widespread areas of mucosal ul life-threatening consequences; u intervention indicated
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-
Vaginal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-
Vaginal perforation	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; intervention indicated
Vaginal stricture	Asymptomatic; mild vaginal shortening or narrowing	Vaginal narrowing and/or shortening not interfering with physical examination	Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination	-

Gastro-intestinal disorders

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Proctitis	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; intervention indicated
Rectal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; intervention indicated
Rectal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; intervention indicated
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; operative intervention indicated
Rectal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention indicated
Rectal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; operative intervention indicated
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-

Renal and urinary disorders

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated	Life-threatening consequences; radiologic or operative intervent indicated
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; radiologic or operative intervent indicated
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; failure; urgent operative interver indicated
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; intervention indicated
Urinary tract pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-

APPENDIX G. FORMS AND PROCEDURES FOR COLLECTING DATA

Form nr	Title	When to complete
1	Randomization Checklist	Before and at registration
2	On Study Form	Immediately after registration
3	Treatment Form	After completion of brachytherapy or EBRT
4	End of Treatment Form	After completion or discontinuation of treatment
5	Toxicity Form	At baseline, completion of brachytherapy, and at each follow-up
6	Follow-up Form	Every 6 months from the date of randomisation until year 5; at year 7 and 10; and at recurrence
7	Recurrence Form	In case of tumor recurrence / progression
8	Serious Adverse Event Form	In case of SAE (<24 h by fax)

Forms 5 and 6 include sections related to EC-related health care use during follow-up

Table for filling out forms

	Time after date of registration/randomization					
Form	**Registration**	**Completion of BT or EBRT**	**End of treatment***	**6-monthly until year 3**	**At year 4 and 5**	**At year 7**
1	**X**					
2	**X**					
3		**X**				
4			**X**			
5	**X**		**X**	**X**	**X**	**(X)**
6				**X**	**X**	**X**
7		**…….…. in case of recurrence …….……...**				
8		**…….…. in case of SAE …….……...**				
QoL	**X**	**X**	**at 6, 12, 18, 24 months and at 3, 5 and 7 years**			

*****3-4 weeks after completion of treatment, or 6 weeks after randomisation in case of observation

APPENDIX H. Checklist for investigations at registration, treatment and follow-up

	Time after date of registration/randomization				
	Before Registration	**2-4 wks after completion of treatment**	**1st - 5th year: every 6 months**	**1st - 5th year: annually**	**5th and 7th year:**
Medical history	X	X	X		X
Physical and pelvic exam	X	X	X		(X)
Vaginal atrophy scoring	X	X		X	
Tumor status	X	X	X		X
Performance status	X	X	X		(X)
Toxicity scoring	X	X	X		
EC-related health care use			X		(X)
Chest X-ray	X			X	
(Planning) CT scan	At first brachytherapy or before EBRT			….. on indication ….	
Quality of Life questionnaire	X	At completion of treatment (resp 6 wks from randomisation in case of observation) and at 6, 12, 18, 24, 36, 60 and 84 months from randomisation; Questionnaires will be sent directly to the patient's home address (unless no consent for this) if no consent: these will be handed out or sent by the patient's study physician or study nurse			