PORTEC-4:
Postoperative Radiation Therapy for Endometrial Carcinoma
Multicenter Randomised Phase III Trial Comparing Vaginal
Brachytherapy (Two Dose Schedules) with Observation after Surgery
A Dutch Gynaecological Oncology Group trial

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Trial website: www.msbi.nl/portec4
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# 1. STUDY SYNOPSIS

<table>
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<tr>
<th>Title</th>
<th>PORTEC-4: Randomised Phase III Trial Comparing Vaginal Brachytherapy (two doses schedules: 21 or 15 Gy HDR in 3 fractions) and Observation after Surgery in patients with Endometrial Carcinoma with High-Intermediate Risk Features</th>
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<tr>
<td>Study Design</td>
<td>Prospective, multicenter, randomized Phase III trial led by the Dutch Platform for Radiation Therapy for Gynecological Tumors and the Dutch Gynaecologic Oncology Group</td>
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<td>Primary Study Objectives:</td>
<td>Establish vaginal recurrence and 5-year vaginal control including treatment for relapse in patients with high-intermediate risk endometrial carcinoma, treated after surgery with vaginal brachytherapy (21 Gy or 15 Gy in 3 fractions), in comparison with no additional treatment</td>
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<td>Primary endpoint: vaginal recurrence</td>
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<td>Second primary endpoint: 5-year vaginal control including treatment for relapse</td>
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<td>Secondary Study Objectives:</td>
<td>Establish and compare the rates of vaginal toxicity, quality of life, pelvic recurrence, and overall and failure-free survival.</td>
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<tr>
<td>Inclusion Criteria FIGO 2009:</td>
<td>Histologically confirmed endometrioid type endometrial carcinoma, FIGO 2009 stage I, with one of the following combinations of substage, age, and grade:</td>
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<tr>
<td></td>
<td>1. Stage IA, any age and grade 3 without lymph-vascular space invasion (LVSI)</td>
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<tr>
<td></td>
<td>2. Stage IB, age 60 years or older and grade 1 or 2</td>
</tr>
<tr>
<td></td>
<td>3. Stage IB, any age, grade 1-2 with documented LVSI</td>
</tr>
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<td></td>
<td>Surgery consisted of Total Abdominal or Laparoscopic Hysterectomy and Bilateral Salpingo-oophorectomy (TH-BSO)</td>
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<td></td>
<td>WHO-performance status 0-2</td>
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<td></td>
<td>Written informed consent</td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td>Any other stage and type of endometrial carcinoma</td>
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<tr>
<td></td>
<td>Histological types papillary serous carcinoma or clear cell carcinoma</td>
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<td></td>
<td>Uterine sarcoma (including carcinosarcoma)</td>
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<td>Previous malignancy (except for non-melanomatous skin cancer) &lt; 5 yrs</td>
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<td>Previous pelvic radiotherapy</td>
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<td>Interval between the operation and start of radiotherapy exceeding 8 weeks</td>
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<tr>
<td>Number of centres:</td>
<td>Unlimited; centres can join the ongoing study after authorization</td>
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<tr>
<td>Number of patients:</td>
<td>500</td>
</tr>
<tr>
<td>Planned duration</td>
<td>5 years of recruitment</td>
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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 16-17 per 10^5/year.1

The large majority of patients are diagnosed at early stage (International Federation of Gynecology and Obstetrics (FIGO) stage I, Appendix A²), 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 stages II-III EC, or with 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.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 1.³⁶ 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) toxicity11. 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%. 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. 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). 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.

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. 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, GOG#249 and GOG#278.

**Vaginal brachytherapy: literature data on dose and fractionation**

Literature data from (mostly retrospective) studies which used vaginal brachytherapy alone in stage 1 endometrial cancer showed that even with modest doses of vaginal brachytherapy, vaginal control rates of over 95% were obtained. Pelvic and distant failure rates and overall survival were similar to those of patients treated with surgery alone. However, most studies included only or mainly low risk (grade 1-2 with <50% invasion) patients.

High vaginal control rates have been reported with a wide range of brachytherapy doses. Traditionally, low-dose-rate (LDR) brachytherapy was used. In view of the clear advantages for patients (short out-patient procedure) and staff (no radiation exposure), virtually all centres have switched to high-dose-rate (HDR) brachytherapy with equal efficacy and very low rates of side effects.

Petereit and Pearcey reviewed the results of HDR-brachytherapy in stage 1 endometrial cancer patients and concluded that a LQED up to 42 Gy at 5 mm (for example, 35 Gy HDR to the surface or 21 Gy to 5 mm depth
PORTEC-4, KWF-CKS UL2011-5336; CME P11.185; version 1.5.1, 09 May 2013

in 3 fractions) provided local control rates of 98% and over. The use of higher doses did not lead to improved
local control, while complication rates were increased. Many different HDR treatment schemes have been
reported. Chadha et al.\textsuperscript{18} and Weiss et al.\textsuperscript{13} both prescribed 3 fractions of 7 Gy (specified, however, at 5 mm
depth and at the surface, respectively) to the upper ½ - 2/3 vagina in 3 weeks, and found excellent vaginal
control rates. In both series high risk patients were included: in Weiss’ series 44 out of 122 patients treated
with TAH-BSO and vaginal brachytherapy had high risk-stage 1 or stage 2 disease, and in Chadha’s study 38
of 124 surgically staged patients were high risk. The vaginal control rates were 98.4 and 100%. Pelvic and
distant relapses were mostly found in high risk-stage 1 and stage 2 patients, yielding 5-year DFS rates of 94%
and 74%, respectively (33). Anderson et al.\textsuperscript{19} used a dose level of 3 fractions of 5 Gy (at 5 mm) in a similar
group of 102 surgically staged patients of which 41 had high risk features. They reported 98% local control
rate and 5-year DFS of 93%. Rittenberg\textsuperscript{12} reported a vaginal recurrence rate of 5.7% in a subset of 51 patients
with stage I EC with deep invasion; compared to 2.3% for the whole group with stage I disease. Five-year
survival was 95%. Use of ovoids is recommended by Pearcey et al.\textsuperscript{14}, prescribing 2 fractions of 16.2 Gy HDR
(specified at the vaginal surface) one week apart, with equivalent vaginal control and complication rates.
Vaginal recurrences were mainly located in the upper vagina, with a ratio of proximal to distal recurrences of
4:1\textsuperscript{20}. Several authors recommend treating only the upper half of the vagina, as this was associated with lower
complication rates (vaginal stenosis and fistula) than when treating the entire length of the vagina.

In a large series of 217 patients reported by Onsrud et al.\textsuperscript{21} who were treated with 22 Gy HDR brachytherapy in
4 fractions of 5.5 Gy, dose specification was either at 5 mm (n=96) or at 3, 4 or 5 mm (n=121), depending on
clinical estimation of the vaginal thickness. Vaginal relapse was similar (1% vs 2.5%), while the rate of late
vaginal reactions grade 1 and 2 were 26% and 8% for specification at 5 mm, vs. 17% and 1% after
individualized specification (p = 0.005). Bladder toxicity grade 1 occurred in 9% vs. 1% (p = 0.005), and rectal
toxicity grade 1 in 5% and 1%, respectively. In a randomized trial reported by Sorbe et al.\textsuperscript{22}, 290 patients with
low-risk EC were treated with 6 fractions of HDR brachytherapy over 8 days, and were allocated to receive
either 15 Gy in 2.5 Gy fractions, or 30 Gy in 5 Gy fractions. The rate of vaginal recurrences in this low-risk
group was 0.7%, without difference between the two randomized groups. The mean vaginal shortening
measured by colpometry was 0.3 cm in the 2.5 Gy group (ns), and 2.1 cm in the 5 Gy group (p < 0.001) at 5
years. Mucosal atrophy and bleeding were significantly more frequent in the 5 Gy group. These data show that
very different doses (equivalent dose for 2 Gy per fraction with $\alpha/\beta$ 3 for late mucosal toxicity of 30 vs 94 Gy at
the mucosal surface, respectively) are effective and that dose is related to vaginal toxicity, however, these
were low-risk patients without current indication for any adjuvant treatment.

**Vaginal brachytherapy in the PORTEC-2 trial**

Based on these 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, LDR and HDR
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.

**Mucosal atrophy**

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. 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. As literature data suggest efficacy of lower dose schedules, the standard dose as used in the PORTEC2 trial should be compared to a somewhat lower dose schedule, to further reduce late effects.

**Remaining questions**

Optimal brachytherapy dose, target length and target depth remain largely unknown. The PORTEC-2 trial has shown that 21 Gy in 3 fractions, prescribed at 5 mm depth to the upper half of the vagina is safe and effective in preventing vaginal recurrence. As the treated length of the vagina was 4 cm in most cases, it seems safe and convenient to define the CTV as the proximal 4 cm and prescribe the active length as 3.5 cm as opposed to a percentage of the vaginal length; with 5 mm on both sides of the CTV this would mean a treated length of 4.5 cm vagina.

Because of the wide range of dose schedules with reported equally effective vaginal control rates, and the higher rates of mucosal atrophic changes in the VBT arm of PORTEC-2, the standard dose schedule of 21 Gy in 3 fractions of 7 Gy could be compared to a lower dose schedule. In view of the fact that there is a variation in surface doses with different vaginal cylinder widths, and that individual estimation of the mucosal thickness as used by Onsrud would cause large interobserver variability, it seems preferable to use standard prescription at 5 mm depth and reduce the dose per fraction. Reducing the fraction dose might further reduce late effects compared to just reducing the total dose. Thus, the best comparison would seem be to 21 Gy in 3 fractions of 7 Gy each with 15 Gy in 3 fractions of 5 Gy each.

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, 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. 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). Observation after surgery in patients with intermediate risk EC has only been
compared to EBRT in randomized trials, and never in a population consisting solely of patients with HIR features. On the other hand, the recurrence and survival rates in the PORTEC-2 trial (including only patients with HIR features) were very similar to those in the older PORTEC-1 trial, which included intermediate risk EC patients with on average more favorable features. The algorithm below has been based on data from the PORTEC-1 trial for patients with HIR features, and from the PORTEC-2 trial.

\textit{Algorithms of alternative management options}

\begin{align*}
  100 & \text{observe} \\
  100 & \text{VBT} \\
  15 & \text{vaginal relapse} \\
  & \text{EBRT + VBT} \\
  12-14 & \text{CR} \\
  & \text{EBRT + VBT} \\
  1-3 & \text{no CR} \\
  & \text{EBRT + VBT or relapse} \\
  2 & \text{vaginal relapse} \\
  & \text{EBRT + VBT} \\
\end{align*}

In conclusion, it would be essential to conduct a trial aiming at both comparing a large group of EC patients with HIR features treated with brachytherapy to a group with observation after surgery, and treatment (EBRT plus VBT) only in case of vaginal recurrence, and comparing two dose levels of vaginal brachytherapy. Furthermore, imaging with CT or MRI with the vaginal cylinder in situ at least at the first brachytherapy session would yield invaluable data on target volume depth and width and doses to rectum and bladder.

\section*{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 (in two brachytherapy dose schedules of 21 or 15 Gy HDR at 5 mm depth in 3 fractions, respectively), compared with no additional treatment after surgery. Second primary objective is to establish overall vaginal control, including salvage treatment for patients with vaginal relapse, at 5 years.

Primary endpoint is vaginal recurrence. Second primary endpoint is the 5-year probability of vaginal control, including treatment for vaginal relapse.

Secondary objectives are to establish and compare the rates of pelvic nodal recurrence; overall and failure-free survival; vaginal toxicity; and quality of life. The objective of the brachytherapy dose comparison is to estimate the differences in vaginal relapse, toxicity and quality of life (with emphasis on sexual symptoms and functioning) between the two dose levels with sufficient precision.

\section*{4. Trial design}

In this multicenter trial, 500 patients with endometrioid type endometrial adenocarcinoma with high-intermediate risk features will be randomised (2:1) to one of the following arms:

1. Vaginal brachytherapy (standard arm); 1:1 randomized to
   a. brachytherapy dose 21 Gy HDR at 5 mm depth, in 3 fractions of 7 Gy each (standard dose)
b. brachytherapy dose 15 Gy HDR at 5 mm depth, in 3 fractions of 5 Gy each

2. Observation (experimental arm)

Primary study endpoint is vaginal relapse; second primary endpoint is 5-year vaginal control including treatment for vaginal relapse. Secondary objectives are pelvic recurrence; overall survival; vaginal toxicity; and quality of life.

Stratification will be done for:
1. participating centre
2. grade (1 vs 2 vs 3)
3. type of surgery (TLH vs TAH; 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 substage, age, and grade:
   a. Stage IA, any age, grade 3 without lymph-vascular space invasion (LVSI)
   b. Stage IB, age 60 years or older and grade 1 or 2
   c. Stage IB, any age, grade 1 or 2 with documented LVSI
2. Surgery consisted of Total Abdominal or Laparoscopic Hysterectomy and Bilateral Salpingo-<Oophorectomy (TH-BSO). Although pelvic lymphadenectomy is not recommended; 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
3. Uterine sarcoma (including carcinosarcoma)
4. Previous malignancy (except for non-melanomatosus 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 vs. 15 Gy HDR in 3 fractions of 5 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 observed after surgery and be followed closely for vaginal recurrence. 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 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-randomization 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-oöphorectomy (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 as 5 or 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 5 or 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 symmetrical in the cranial-caudal direction, and chosen in such as 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%. The most caudal dwell position is placed 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 4.5 cm.

At 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 4 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 all fractions, and dose distributions for the CTV and OAR should be recorded, and the 2cc EQD2 doses in the OAR should be calculated for documentation and evaluation purposes. If feasible, CT scanning may be repeated at subsequent fractions to evaluate interfraction variations, and cumulative dose distributions recorded.

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 Treatment for vaginal recurrence
Patients with vaginal recurrence (without distant metastases) will be treated promptly with external beam RT (dose 45-50.4 Gy in 1.8-2 Gy fractions) followed by a brachytherapy boost (3 x 6-7 Gy HDR, preferably with MRI-based planning), aiming at a total dose of 80 Gy EQD2 dose (with $\alpha/\beta=10$) in 90% of the tumor volume. 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 blunt needles through the ovoids 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 $\alpha/\beta=3$) for organs at risk: bladder < 90 Gy, rectum and sigmoid < 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 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, the specimens should be reviewed by the reference pathologist at the regional gynaecologic oncology centre, and this diagnosis will determine final eligibility and entry in the study. 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 a copy of the pathology report for review to one of the regional reference pathologists (section 8.2). The reference pathologist will send final diagnosis within one week, after which eligibility can be determined and the patient can be informed about the study. 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
- size of the tumor (maximal diameter and thickness)
- invasion to < 50% or $\geq$ 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 cornuae and 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 25% (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 mucosa in the cornuae
- 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 diagnosis (no immunohistochemistry).

**8.2. Tissue specimen collection**
Initial pathology review will be conducted by the regional gynaecologic pathologists (as appointed for each participating center) to determine eligibility of a patient for the study. In addition to the review of the histopathologic diagnosis and grading, the results of the reviews will be used to analyze the reproducibility of tumor grading, depth and pattern of myometrial invasion, and lymph-vascular space invasion.
After inclusion of a patient in the trial and obtaining informed consent, the regional pathologist will be requested to send the representative histopathological slides and a separate paraffin-embedded sample of the tumor for the study purposes. The slides will be used for central review, and be returned to the centre after review. The tumor blocks will be saved in a dedicated tissue bank for translational research (see 8.3)

**8.3 Translational research**
Paraffin embedded tissue blocks (1 cm³) from both the endometrial biopsies and surgical specimens, and serum samples will be collected from all consenting patients and archived for translational research.
The focus of research will be to determine and validate newly identified prognostic markers as compared to known prognostic markers in our study population. The aim of these studies will be to define prognostic markers which discriminate between patients who may safely be followed after surgery, and who might benefit from local or of systemic treatment, in other words to further individualise treatment schedules. The second goal of translational research will be to define new molecular targets for treatment.

**9. Follow-up, toxicity evaluation and adverse events**

**9.1. Follow-up**
At the completion of brachytherapy, an end-of-brachytherapy follow up visit after 3-4 weeks should be planned by the radiation oncologist. At this visit, acute vaginal toxicity will be assessed and the end-of-treatment vaginal length and width will be measured. 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 vaginal effects will be done, and the QoL questionnaires will be sent to the patients at the same time intervals. Specifically, late vaginal toxicity will be assessed and the vaginal length and width will be measured once a year.

Long-term outcome evaluation at 7 and 10 years should be obtained, preferably by follow-up visits, 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

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, randomization 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 summarized on the randomization 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 with stratification by participating centre, tumor grade and type of surgery. The trial number and result of randomisation will be obtained via the Internet randomization system and confirmed by email.

10.3. Datamonitoring 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. Limited on-site monitoring will be done by IKNL monitors, at least once in each centre.

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 randomization in the NAT arm) and at 6, 12, 18, 24, 36 and 60 months and at 7 and 10 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 1700 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 150 patients per year.

The study is based on a recruitment period of 4 years, and a follow-up duration of 24 months after inclusion of the last patient before definite analysis. It is expected that the yearly accrual rate will be 150 patients. Thus, a total of 500 patients may be accrued in a 4-year period.

Based on data from the PORTEC-1 and PORTEC-2 trials, the expected 5-year rates of vaginal recurrence will be 2% in the vaginal brachytherapy arm and 10% in the NAT arm. If assuming a minor increase of VR in the patients receiving the lower brachytherapy dose to 3%, this would add to 2.5% VR in the combined brachytherapy arms. The principal aim of the trial is to detect with 90% power this 7.5% difference (2.5 vs 10%, hazard ratio for VBT with respect to NAT 0.24) in vaginal recurrence rate between the combined brachytherapy and control arms. An additional aim of the study is to estimate the difference in VR between the two brachytherapy groups with sufficient precision. Assuming as above that the 5-yr VRR equals 2% in the higher-dose VBT arm and 3% in the lower-dose VBT arm, 167 subjects in each arm ensure that with 80% probability the standard error of the difference in cumulative incidences of VRR at 3 years is below 2.5% and that with 93% probability this standard error is below 3%. With an accrual period of 4 years and additional follow-up of 2 years, the number required for the trial would be 493 patients, and the target will thus be 500. If within the accrual period of 4 years a greater number can be included (600, for 200 in each group), this will be allowed to strengthen the results and enable analysis of subgroups (grade 1-2 LVSI negative vs grade 1-2 LVSI positive vs grade 3).
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.

Interim analyses are planned after reaching one-third (n=167) and two-thirds (n=333) of the required number of 500 eligible patients. At each interim analysis a detailed report will be generated and presented to the DSMB. The 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 for 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, but the following guidelines apply.

1. Proven superiority of the vaginal brachytherapy arms at the first and second interim analyses with alpha levels of 0.0002 and 0.012, respectively, is considered a reason for early stopping of the trial. The final analysis will then be performed with a nominal alpha of 0.0463. It might be considered, depending on data and events, to continue with the 2 brachytherapy arms.

2. If at the first and second interim analyses futility is suggested, i.e. if the lower limit of the confidence interval for the hazard ratio of the VBT arm with respect to NAT corresponding to the appropriate alpha level used in the interim analysis is at least 1.0, this is considered a reason for early stopping of the trial for futility.

12.3 Statistical analysis
All analyses concerning treatment effects will be done according to the intention-to-treat principle. The main endpoints for the comparison of the two treatment arms is vaginal recurrence; second main endpoint is final (5-year) vaginal control including treatment for vaginal relapse. Secondary objectives are pelvic nodal recurrence; overall survival; vaginal toxicity; and quality of life.

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 risks method (with death as competing risk) will be used for analysis of the rates of VR, PR, LRR, and DM. 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.

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. As the PORTEC-4 trial involves comparison of standard adjuvant
brachytherapy to no further treatment after surgery, additional trial insurance is not required, as determined by the Central Ethical Committee.

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 study coordinators, investigators from the participating centres who have included more than 10% 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. 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 centres and local investigators

16.1. The Netherlands - DGOG

1. Academic Medical Center Amsterdam (L. Stalpers) 3-5
2. Arnhem Radiotherapy Institute ARTI (E. van der Steen-Banasik) 10
3. Catharina Hospital Eindhoven (H. van den Berg) 5-10
4. Institute Verbeeten Tilburg (K. De Winter) 10-15
5. Erasmus Medical Center Rotterdam (J.W. Mens) 10-15
6. Leiden University Medical Center (R. Nout, C.L. Creutzberg) 8-10
7. NKI/Antoni v. Leeuwenhoekhuis (M. Bloemers) 8-10
8. MAASTRicht Radiation Oncology Clinic (L. Lutgens) 10-15
9. Medical Spectre Twente, Enschede (J. Jobsen) 10-12
10. Radiotherapy Centre West, Den Haag (T. Stam) 5
11. Radiotherapy Institute Friesland (A. Slot) 8-10
12. Radiotherapy Institute Stedendriebeek (S. van de Pol) 5
13. Sophia Hospital Zwolle (L. Zwanenburg) 5
14. University Medical Center Groningen (B. Pras) 5-10
15. University Medical Center Radboud (A. Snyers) 5-8
16. University Medical Center Utrecht (I. Jürgenliemk-Schulz) 12-15
17. VU Medical Center (O. Meijer) included with AMC/AvL
18. Zeeuws Radiotherapy Institute (V. Coen) 3-5
REFERENCES

10. Cohn DE, Horowitz NS, Mutch DG, et al: Should the presence of lymphvascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? Gynecol Oncol 87:243-246, 2002


APPENDIX A. SUMMARY PORTEC-4

Endometrial carcinoma

Surgery and pathology diagnosis

FIGO 2009:
Stage IA, grade 3, any age, no LVSI
Stage IB, grade 1-2 and age ≥ 60
Stage IB, grade 1-2, any age and LVSI+

Radiation oncologist: eligibility
Pathology review: confirm pathology diagnosis
Informed consent procedure
Baseline quality of life

Randomisation

Vaginal brachytherapy 3x7 Gy HDR at 5 mm

Vaginal brachytherapy 3x5 Gy HDR at 5 mm

EBRT+VBT in case of vaginal recurrence

Follow-up and Quality of Life
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)

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

International Society of Gynecologic Pathologists Classification for Endometrial Carcinomas

1. Endometrial adenocarcinoma
   Papillary/villoglandular
   Secretory
   Ciliated cell
   Adenocarcinoma with squamous differentiation

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 endometrioid carcinomas and mixed clear cell and endometrioid carcinomas should be classified as serous or clear cell carcinomas if they contain at least 25% 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 active length. Active length is the distance between the first (most cranial) and the last active 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 anisotropy) 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 and the prescription point A2 is half way the active length which, in this case, is 17.5 mm. All of these points receive 100% of the prescribed dose, except for A4 at which level 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%.

On the next page, typical dose distributions are shown for cylinders of 35 and 30 mm width, respectively.
Dose distributions for vaginal cylinders of 30 and 35 mm width, respectively. The isodose lines depict the 200% (light blue), 150% (light green, at the surface of the applicator), 100% (red), 75% (pink), 50% (green) and 25% (blue) isodoses.

Compare the reference points to Figure 1 on previous page:

- a = applicator point A1
- c = applicator point A3
- b = applicator point A2
- d, e, f are applicator points A4, A5, A6

- Reference Volume Width (max width of the 100% isodose in mm)
- Reference Volume Length (max length of the 100% isodose in mm)
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](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)


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:

#### Reproductive system and breast disorders

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

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

### Renal and urinary disorders

<table>
<thead>
<tr>
<th>CTCAE v4.0 Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cystitis noninfective</strong></td>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
<td>Symptomatic; medical intervention indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL; tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated</td>
<td>Life-threatening consequences; intervention indicated</td>
</tr>
<tr>
<td><strong>Hematuria</strong></td>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
<td>Symptomatic; medical intervention indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL; tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated</td>
<td>Life-threatening consequences; intervention indicated</td>
</tr>
<tr>
<td><strong>Urinary frequency</strong></td>
<td>Present</td>
<td>Limiting instrumental ADL; medical management indicated</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Urinary incontinence</strong></td>
<td>Occasional (e.g., with coughing, sneezing, etc.), pads not indicated</td>
<td>Spontaneous; pads indicated; limiting instrumental ADL</td>
<td>Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL</td>
<td>-</td>
</tr>
<tr>
<td><strong>Urinary retention</strong></td>
<td>Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual</td>
<td>Placement of urinary, suprapubic or intermittent catheter placement indicated; medical intervention indicated</td>
<td>Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass</td>
<td>Life-threatening consequences; failure; urgent operative intervention indicated</td>
</tr>
<tr>
<td><strong>Urinary tract obstruction</strong></td>
<td>Asymptomatic; clinical or diagnostic observations only</td>
<td>Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated</td>
<td>Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective radiologic, endoscopic or operative intervention indicated</td>
<td>Life-threatening consequences; intervention indicated</td>
</tr>
<tr>
<td><strong>Urinary tract pain</strong></td>
<td>Mild pain</td>
<td>Moderate pain; limiting instrumental ADL</td>
<td>Severe pain; limiting self care ADL</td>
<td>-</td>
</tr>
<tr>
<td><strong>Urinary urgency</strong></td>
<td>Present</td>
<td>Limiting instrumental ADL; medical management indicated</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
APPENDIX G. QUALITY OF LIFE QUESTIONNAIRE (ENGLISH)

**EORTC QLQ-C30** (version 3)  

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your first initial:  
Your birth date (Day, Month, Year):  
Today’s date (Day, Month, Year):

<table>
<thead>
<tr>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Do you have any trouble taking a long walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Do you have any trouble taking a short walk outside of the house?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Do you need to stay in bed or a chair during the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Do you need help with eating, dressing, washing yourself or using the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**During the past week:**

<table>
<thead>
<tr>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Were you limited in doing either your work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Have you had pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Have you had trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Have you felt weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Have you vomited?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please go on to the next page
### During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. Have you been constipated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. Have you had diarrhea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Did pain interfere with your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had difficulty in concentrating on things,</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>like reading a newspaper or watching television?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment interfering with your family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment interfering with your social activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment caused you financial difficulties?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**For the following questions please circle the number between 1 and 7 that best applies to you:**

29. How would you rate your overall health during the past week?

   1  2  3  4  5  6  7

   **Very poor**  **Excellent**

30. How would you rate your overall quality of life during the past week?

   1  2  3  4  5  6  7

   **Very poor**  **Excellent**
Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems.

### During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. Have you had swelling in one or both legs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32. Have you felt heaviness in one or both legs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33. Have you had pain in your lower back and / or pelvis?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34. When you felt the urge to pass urine, did you have to hurry to get to the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35. Have you passed urine frequently?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36. Have you had leaking of urine?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37. Have you had pain or a burning feeling when passing urine?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38. When you felt the urge to move your bowels, did you have to hurry to get to the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39. Have you had any leakage of stools?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40. Have you been troubled by passing wind?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41. Have you had cramps in your abdomen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>42. Have you had a bloated feeling in your abdomen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43. Have you had tingling or numbness in your hands or feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>44. Have you had aches or pains in your muscles or joints?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45. Have you lost hair?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46. Has food and drink tasted differently from usual?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>47. Have you felt physically less attractive as a result of your disease or treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please go on to the next page
### During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>48. Have you felt less feminine as a result of your disease or treatment?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. Hebt u momenteel een partner?</td>
<td>Ja</td>
<td>Nee</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### During the past 3 months:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>50. To what extent were you interested in sex?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>51. To what extent were you sexually active?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>52. If you have not been sexually active, please provide the reason:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- I do not have a partner (anymore)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- In our relationship sexuality is not important (anymore)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Medical reasons of my partner</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Due to my illness / treatment</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Answer these questions only if you have been sexually active during the past 3 months:**

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>53. Has your vagina felt dry during sexual activity?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>54. Has your vagina felt short and / or tight?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>55. Have you had pain during sexual intercourse or other sexual activity?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>56. Was sexual activity enjoyable for you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

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QUALITY OF LIFE QUESTIONNAIRE (Dutch Version)

EORTC QLQ-C30 (versie 3)

Wij zijn geïnteresseerd in bepaalde dingen over u en uw gezondheid. Wilt u alle vragen zelf beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is. Er zijn geen "juiste" of "onjuiste" antwoorden. De informatie die u geeft zal strikt vertrouwelijk worden behandeld.

Wilt u uw voorletters invullen:  |  |  |  |
Uw geboortedatum (Dag, Maand, Jaar):  |  |  |  |  |  |  |
De datum van vandaag (Dag, Maand, Jaar):  |  |  |  |  |  |  |

<table>
<thead>
<tr>
<th></th>
<th>Helemaal niet</th>
<th>Een beetje</th>
<th>Nogal</th>
<th>Heel erg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heeft u moeite met het doen van inspannende activiteiten zoals het dragen van een zware boodschappentas of een koffer?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Heeft u moeite met het maken van een lange wandeling?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Heeft u moeite met het maken van een korte wandeling buitenshuis?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Moet u overdag in bed of in een stoel blijven?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Heeft u hulp nodig met eten, aankleden, u zelf wassen of naar het toilet gaan?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Gedurende de afgelopen week:

<table>
<thead>
<tr>
<th></th>
<th>Helemaal niet</th>
<th>Een beetje</th>
<th>Nogal</th>
<th>Heel erg</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Was u beperkt bij het doen van uw werk of andere dagelijkse bezigheden?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Was u beperkt in het uitoefenen van uw hobbies of bij andere bezigheden die u in uw vrije tijd doet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Was u kortademig?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Heeft u pijn gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Had u behoefte te rusten?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Heeft u moeite met slapen gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Heeft u zich slap gevoeld?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Heeft u gebrek aan eetlust gehad?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Heeft u zich misselijk gevoeld?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Wilt u a.u.b. naar de volgende bladzijde gaan
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>Helemaal niet</th>
<th>Een beetje</th>
<th>Nogal</th>
<th>Heel erg</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.</td>
<td>Heeft u overgegeven?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td>Had u last van obstipatie? (Was u verstopt?)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>Had u diarree?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>Was u moe?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>Heeft pijn u gehinderd in uw dagelijkse bezigheden?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>Heeft u moeite gehad met het concentreren op dingen, zoals een krant lezen of televisie kijken?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>21.</td>
<td>Voelde u zich gespannen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>22.</td>
<td>Maakte u zich zorgen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>23.</td>
<td>Voelde u zich prikkelbaar?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>24.</td>
<td>Voelde u zich neerslachtig?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>25.</td>
<td>Heeft u moeite gehad met het herinneren van dingen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>26.</td>
<td>Heeft uw lichamelijke toestand of medische behandeling uw <strong>familieleven</strong> in de weg gestaan?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>27.</td>
<td>Heeft uw lichamelijke toestand of medische behandeling u belemmerd in uw <strong>sociale</strong> bezigheden?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>28.</td>
<td>Heeft uw lichamelijke toestand of medische behandeling financiële moeilijkheden met zich meegebracht?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Wilt u voor de volgende vragen het getal tussen 1 en 7 omcirkelen dat het meest op u van toepassing is:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>Helemaal niet</th>
<th>Een beetje</th>
<th>Nogal</th>
<th>Heel erg</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.</td>
<td>Hoe zou u uw algehele <strong>gezondheid</strong> gedurende de afgelopen week beoordelen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Erg slecht</td>
<td></td>
<td>Uitstekend</td>
<td></td>
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</tr>
<tr>
<td>30.</td>
<td>Hoe zou u uw algehele &quot;<strong>kwaliteit van het leven</strong>&quot; gedurende de afgelopen week beoordelen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Erg slecht</td>
<td></td>
<td>Uitstekend</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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Soms melden patiënten dat ze de volgende symptomen of problemen hebben. Wilt u aangeven in welke mate u deze symptomen of problemen heeft ervaren?

<table>
<thead>
<tr>
<th></th>
<th>Gedurende de afgelopen week:</th>
</tr>
</thead>
<tbody>
<tr>
<td>31.</td>
<td>Had u opgezette benen (zwelling van een of beide benen)?</td>
</tr>
<tr>
<td>32.</td>
<td>Had u een zwaar gevoel in een of beide benen?</td>
</tr>
<tr>
<td>33.</td>
<td>Had u pijn in uw onderrug en/of bekken?</td>
</tr>
<tr>
<td>34.</td>
<td>Moest u zich zodra u aandrang voelde om te plassen naar het toilet haasten?</td>
</tr>
<tr>
<td>35.</td>
<td>Moest u vaak plassen?</td>
</tr>
<tr>
<td>36.</td>
<td>Had u onvrijwillig urineverlies (ongelukjes)?</td>
</tr>
<tr>
<td>37.</td>
<td>Had u pijn of een brandend gevoel toen u plaste?</td>
</tr>
<tr>
<td>38.</td>
<td>Moest u zich zodra u aandrang voelde voor ontlasting naar het toilet haasten?</td>
</tr>
<tr>
<td>39.</td>
<td>Hebt u onbedoeld ontlasting verloren?</td>
</tr>
<tr>
<td>40.</td>
<td>Had u last van winderigheid?</td>
</tr>
<tr>
<td>41.</td>
<td>Had u buikkramen?</td>
</tr>
<tr>
<td>42.</td>
<td>Had u een opgeblazen gevoel in uw buik?</td>
</tr>
<tr>
<td>43.</td>
<td>Had u een tintelend/prikkelend of doof gevoel in uw handen of voeten?</td>
</tr>
<tr>
<td>44.</td>
<td>Had u pijn in uw spieren of gewrichten?</td>
</tr>
<tr>
<td>45.</td>
<td>Had u haaruitval?</td>
</tr>
<tr>
<td>46.</td>
<td>Smaakten voedsel en drank anders dan gewoonlijk?</td>
</tr>
<tr>
<td>47.</td>
<td>Voelde u zich lichamelijk minder aantrekkelijk ten gevolge van uw ziekte of behandeling?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Helemaal niet</th>
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<tr>
<td>47</td>
<td>1</td>
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</tr>
</tbody>
</table>

Wilt u a.u.b. naar de volgende bladzijde gaan
Gedurende de afgelopen week:

48. Voelde u zich minder vrouwelijk ten gevolge van uw ziekte of behandeling?

49. Hebt u momenteel een partner? □ Ja □ Nee

Gedurende de afgelopen drie maanden:

50. In hoeverre had u zin in seks?

51. In hoeverre bent u seksueel actief geweest?

52. Indien u niet seksueel actief bent geweest, wilt u hier de reden aankruisen?
   □ Ik heb geen partner (meer)
   □ In onze relatie is seksualiteit niet (meer) belangrijk
   □ Medische reden bij mijn partner
   □ Door mijn ziekte / behandeling

De onderstaande vragen alleen beantwoorden indien u seksueel actief was gedurende de afgelopen 3 maanden:

53. Voelde uw vagina droog aan tijdens de gemeenschap?

54. Voelde uw vagina korter en/of nauwer aan?

55. Had u pijn tijdens de gemeenschap?

56. Was seks plezierig voor u?
APPENDIX H.  PATIENT INFORMATION (DUTCH)

Patienteninformatie ten behoeve van een wetenschappelijk onderzoek:

PORTEC-4, een onderzoek naar de waarde van inwendige bestraling (brachytherapie) en optimale dosis daarvan bij patiënten met baarmoederkanker (endometriumcarcinoom).

Geachte mevrouw,

U bent gevraagd om deel te nemen aan een wetenschappelijk onderzoek. U hebt hierover een gesprek met uw arts gehad. Deze schriftelijke informatie is bedoeld als herhaling en aanvulling op wat uw arts heeft uitgelegd. Voor u een beslissing neemt is het belangrijk dat u deze informatie goed leest.

Wat is het doel van de studie?

Kort geleden bent u geopereerd door de gynaecoloog voor baarmoederkanker (endometriumcarcinoom). Bij deze operatie zijn in ieder geval uw baarmoeder en eierstokken verwijderd, met als resultaat dat alle zichtbare kanker is weggenomen. We weten dat sommige patiënten een wat lager of juist wat hoger risico hebben dat de kanker op een later moment terug komt. Dit kan worden ingeschat op basis van het weefselonderzoek na de operatie. Hierbij is gebleken dat bij u de kans op terugkeer licht verhoogd is. Uit eerder onderzoek is bekend dat de kans op plaatselijke terugkeer van de baarmoederkanker wordt verminderd door radiotherapie (bestraling), en uw arts heeft u daarom verwezen naar de radiotherapeut- oncoloog.

De standaard behandeling bestaat uit 3 inwendige bestralingen op het binnenste deel van de vagina (schede), die met behulp van een cilinder worden uitgevoerd. Dit is een gladde, op uw maat aangepaste cilinder die met gel wordt ingesmeerd zodat deze gemakkelijk in de vagina kan worden ingebracht. Dit is niet pijnlijk, wel geven vrouwen aan het ongemakkelijk te vinden. Uit eerder onderzoek is bekend dat deze inwendige bestralingen de kans op plaatselijke terugkeer in de vagina verlagen van ongeveer 10-15% zonder bestraling, tot ongeveer 2% na 5 jaar. Er is geen verschil in kans op terugkeer elders, noch op de uiteindelijke overlevingskansen. Door de inwendige bestraling kunnen vrouwen op wat langere termijn meer droogte en stugheid van het bovenste (meest binnenin gelegen) deel van de schede krijgen (bij ongeveer 25% van de patienten), en soms enige vernauwing en/of verkorting (bij 2 tot 3%). Andere bijwerkingen zijn zeer zeldzaam, en kunnen bestaan uit vaker aandrang voor ontlasting en/of plassen in de eerste dagen na de behandeling.

Uit andere, kleinere onderzoeken blijkt dat bestraling met een lagere dosis ook effectief lijkt te zijn, waarbij de lagere dosis minder kans op bijwerkingen lijkt te hebben. Aangezien de overlevingskansen gelijk zijn voor behandeling met en zonder bestraling, en aangezien een plaatselijke terugkeer in de vagina goed te behandelen is, lijkt er met de huidige standaard behandeling sprake te zijn van overbehandeling. Nu worden immers alle vrouwen inwendig bestraald met de bijwerkingen en het ongemak die daarbij horen, om bij een kleine groep plaatselijke terugkeer te voorkomen. Voor behandeling bij plaatselijke terugkeer is wel een combinatie van uitwendige bestralingen en inwendige bestraling nodig, wat betekent dat de behandeling dan intensiever is, en meer kans op bijwerkingen van darmen en blaas geeft. Het voordeel is dat veel minder vrouwen (10-15 van de 100) bestraald moeten worden.

Het doel van de studie is te onderzoeken of de standaard toepassing van 3 inwendige bestralingen de kans op plaatselijke terugkeer dermate verkleint, dat dit behandeling van alle patiënten rechtvaardigt, of dat het beter is patiënten onder observatie te houden en alleen behandeling te geven aan de kleine groep vrouwen waarbij de kanker daadwerkelijk terugkeert. Daarnaast wordt de standaard dosis van inwendige bestraling vergeleken met een iets lagere dosis. Hierbij wordt gelet op de resultaten van de behandeling (een zo laag mogelijke kans op terugkeer van de ziekte), maar ook op de bijwerkingen van de behandelingen en de “kwaliteit van leven” die u ervaart.
Het betreft een fase 3 (vergelijkend) onderzoek.

**Wat betekent de studie voor mij?**
Als u besluit mee te doen aan het onderzoek, wordt door middel van loting bepaald welke behandeling u krijgt:

- een serie van 3 inwendige bestralingen, gegeven in 2 weken tijd (standaard behandeling, met standaard dosis)
- een serie van 3 inwendige bestralingen, gegeven in 2 weken tijd (standaard behandeling, met lagere dosis), óf
- geen verdere behandeling, maar regelmatige controle.

Van de 3 vrouwen krijgen er dus 2 inwendige bestraling, en 1 krijgt nauwgezette controle. Van de 2 vrouwen die inwendige bestraling loten, krijgt 1 de standaard dosis en 1 de lagere dosis. Deze loting (randomisatie) is om gelijke groepen te krijgen, wat nodig is om de uitkomst van de behandelingen later goed te kunnen vergelijken. Noch uzelf, noch uw artsen kunnen bepalen welke van de twee behandelingen u krijgt.

**Wat houdt inwendige bestraling in?**

In totaal krijgt u 3 van dergelijke inwendige bestralingen, met tussenpoos van 3 tot 7 dagen. De behandeling zal de eerste keer in totaal ongeveer een uur duren, omdat er na het inbrengen van de cilinder een CT scan van het bekkengebied wordt gemaakt voor het berekenen van de bestraling. De tweede en derde behandelingen duren meestal korter, ongeveer een half uur, omdat de berekening en scan van de eerste keer gebruikt kunnen worden.

**Wat zijn de bijwerkingen van inwendige bestraling?**
Doorgaans hebt u weinig tot geen klachten na de inwendige bestraling. Soms is het plassen een tot enkele dagen wat gevoelig, en u kan wat vaker aandrang voor plassen of ontlasting hebben. U kunt het beste veel blijven drinken. Soms treedt er licht bloedverlies op gedurende 1 tot enkele dagen; dit gaat vanzelf over.

Kort na de bestralingen kunt u weer gewoon vrijen en gemeenschap hebben. Door de gegeven bestraling kan het bovenste (meest binnenin gelegen) deel van uw vagina van binnen geleidelijk droger en wat stugger worden (bij ongeveer 25% van de vrouwen) dan tevoren, en in zeldzame gevallen (2-3%) ook wat nauwer of korer. Het is aan te raden om bij de eerste keren glijmiddel (Sensilube of K-Y gel, bij de drogist verkrijgbaar) te gebruiken. Mocht u geen (regelmatige) gemeenschap hebben en zoveel mogelijk willen voorkomen dat de vagina na de bestraling geleidelijk wat stugger wordt, dat kunt u zonodig uw vagina regelmatig wat oprekken met een setje cilinders (pelottes). Uw radiotherapeut zal dit met u bespreken.

Verder geven sommige vrouwen aan kortdurend last te hebben van lichte vermoeidheid.

**Wat houdt “kwaliteit van leven” onderzoek in?**
Het kwaliteit van leven onderzoek bestaat uit een vragenlijst, die u voorafgaand aan de behandeling, na het einde van de bestraling, en dan na 6, 12 en 18 maanden, en na 2, 3, 5, 7 en 10 jaar (gerekend vanaf het begin van de behandeling) invult. Met deze vragenlijsten wordt de kwaliteit van leven, zoals u dat zelf ervaart, gemeten. Uzelf kunt namelijk het beste beoordelen hoe zwaar de behandeling is en wat de gevolgen zijn voor uw welbevinden. De kwaliteit van leven vragenlijst bestaat uit een algemeen gedeelte van 30 vragen, en een specifiek gedeelte (eveneens 30 vragen). Het invullen zal ongeveer 10-15 minuten duren.

De eerste vragenlijst krijgt u van uw radiotherapeut. Daarbij zit een adresformulier met de vraag of u het goed vindt dat de volgende vragenlijsten rechtstreeks vanuit het coördinerende centrum naar uw
huisadres worden gestuurd. Indien u daarin toestemt, stuurt u de lijst met uw adresgegevens terug. U krijgt dan de volgende keren de vragenlijst thuis toegestuurd, en u kunt deze terugsturen in een gratis antwoordenveloppelte.

De naam- en adresgegevens die u voor het kwaliteit van leven onderzoek invult, worden in een apart computerbestand bewaard dat alleen voor het toezenden van de vragenlijsten gebruikt wordt. Dit bestand maakt geen deel uit van de overige (gecodeerde) gegevens die voor het onderzoek worden bewaard.

De antwoorden op de vragenlijsten worden i.v.m. de privacy met grote zorg behandeld. Bij ontvangst van de lijsten worden de gegevens anoniem gemaakt en onder code bewaard, zodat ze later bij de bewerking niet herleidbaar zijn.

Voor de studie is het van groot belang dat u iedere lijst invult en opstuurt. Als het studiecentrum ze niet van u terug ontvangt, wordt u (schriftelijk) benaderd met de vraag dit alsnog te doen. Als u liever niet meer mee wilt werken, staat het u uiteraard altijd vrij zich terug te trekken. Dit kunt u dan op het formulier aangeven.

**Wat gebeurt er na de behandeling?**
Na de behandeling zult u om en om controle afspraken krijgen bij uw gynaecoloog en uw radiotherapeut. De eerste twee jaar zullen deze controles om de 3 maanden zijn, daarna om de 6 maanden, en na 5 jaar ieder jaar.

De controle bestaat vooral uit het informeren hoe het met u gaat en of u klachten heeft, en lichamelijk onderzoek (onderzoek van de buik en inwendig onderzoek). Eén keer per jaar wordt er een longfoto gemaakt. Dit zijn onderzoeken die ook plaatsvinden als u niet aan de studie meedoet, alhoewel niet alle centra jaarlijks een longfoto zouden maken. Andere onderzoeken, zoals een CT scan, worden alleen gedaan als daar een aanleiding voor is.

**Moet ik aan de studie meedoen?**

Als u besluit niet mee te doen aan het onderzoek, wordt in principe de standaard behandeling, inwendige bestraling met de standaard dosis, geadviseerd.

**Wat zijn de mogelijke voordelen en nadelen van deelname?**
Er is geen verschil in de (kleine) kans op terugkeer van de kanker elders in het lichaam, noch op de uiteindelijke (hoge) overlevingskans tussen de behandelingsgroepen.

Als u in de groep komt die inwendige bestraling krijgt, kunnen de bijwerkingen optreden die hierboven genoemd zijn. Bij de lagere dosis zal de kans hierop wat lager zijn. De kans op plaatselijke terugkeer is laag, onder de 2% na 5 jaar. Dat wil zeggen dat van de 100 vrouwen die inwendig bestraald worden, er bij 1 tot 2 de kanker plaatselijk, in de vagina, terugkeert.

Als u in de groep komt die geen bestraling krijgt, worden u het ongemak en bijwerkingen van de inwendige bestralingen bespaard: 85 tot 90 van de 100 vrouwen hoeven nooit bestraald te worden. De kans op plaatselijke terugkeer is wat hoger: ongeveer 10-15% na 5 jaar, dat wil zeggen dat van de 100 vrouwen die gecontroleerd worden, er bij 10 tot 15 de kanker plaatselijk, in de vagina, terugkeert. Deze vrouwen worden dan doorgaans behandeld met uitwendige bestraling en inwendige bestraling, waarbij de grote meerderheid (8-9 van de 10) alsnog genezen wordt. Deze combinatie van uitwendige en inwendige bestralingen geeft wel meer kans op bijwerkingen van de darmen en/of van de blaas. Er is ongeveer 15% kans op aanhoudende, vaak wisselende darmklachten (vaker en sterkere drang, soms diarhée, in buurt van toilet willen blijven), en 10-15% kans op blaasklachten (vaker drang, vaker enig urine verlies).

De uiteindelijke kans dat de ziekte in de vagina onder controle blijft is dus in alle groepen even groot (98 van de 100 patiënten). Voor de 2% (2 van de 100 patiënten) waarbij de kanker toch terugkeert hangt de verdere behandeling erg af van de situatie. De behandeling kan dan bestaan uit een operatie, uit hormoonbehandeling als de tumor daarvoor gevoelig is, hernieuwde uitwendige of inwendige bestraling, chemotherapie of een combinatie van een of meer van deze behandelingen.
Moet ik meteen beslissen?
Neemt u rustig enige bedenktijd voordat u beslist of u meedoet of niet. U kunt deze informatie dan nog eens bespreken met uw partner, familie, huisarts of met uw gynaecoloog. Aarzel niet uw vragen met uw behandelend arts(en) te bespreken.

Worden mijn gegevens vertrouwelijk behandeld?
U kunt ervan verzekerd zijn dat alle gegevens, die tijdens het onderzoek verzameld worden, vertrouwelijk behandeld worden. Behalve uw behandelend arts(en) zullen alleen bevoegde personen die onder toezicht van de behandelend arts staan, uw gegevens kunnen inzien.
De gegevens die voor het onderzoek worden bewaard, zullen worden gecodeerd voor ze naar het centrale computerbestand worden gestuurd. Dit betekent dat de gegevens onder code worden ingestuurd en bewaard, en alleen in uw eigen ziekenhuis (bij uw arts en daartoe bevoegde personen) bekend is welke medische gegevens bij die code horen.
Naast gegevens over de inwendige bestraling, eventuele bijwerkingen, en het beloop na de behandeling, zullen medische gegevens over de operatie en het weefselonderzoek van de baarmoederkanker geregistreerd worden. Een stukje van het weefsel, waarop de diagnose baarmoederkanker gesteld is, wordt ter bevestiging van de diagnose naar het centrale pathologielaboratorium van uw regio gestuurd. Wij lichten uw huisarts in over uw deelname aan dit onderzoek, tenzij u daar bezwaar tegen aangeeft.
Gegevens of resultaten met betrekking tot het onderzoek worden in anonieme vorm verwerkt. De resultaten van dit onderzoek kunnen gebruikt worden in wetenschappelijke publicaties, maar ook dan zijn uw persoonlijke gegevens niet herkenbaar. U kunt aangeven of u na beëindigen van het onderzoek, een brief met de belangrijkste resultaten wenst te ontvangen.

Wordt een stukje weefsel bewaard?
Een heel klein gedeelte (1 cm³) van het tumorweefsel zal onder code in het centrale pathologielaboratorium worden bewaard voor wetenschappelijk onderzoek. Het betreft hier onderzoek naar nieuwe eigenschappen van het weefsel dat een voorspellende waarde kunnen hebben voor het resultaat van de behandeling en/of het beloop van de ziekte. Hiermee hopen we in de toekomst de behandeling nog verder te kunnen verbeteren, en preciezer te kunnen uitmaken welke patiënten baat van de behandelingen zullen hebben. Het weefselstukje zal uitsluitend worden gebruikt voor aanvullend wetenschappelijk onderzoek dat past binnen de vraagstelling van deze studie, of hieruit voortvloeit, en betrekking heeft op baarmoederkanker. Mocht u bezwaar hebben tegen het bewaren van het stukje weefsel, dan kunt u dit apart op de toestemmingsverklaring aangeven.

Is er een verzekering voor deze studie?
Aangezien het in deze studie gaat om vergelijking van standaard behandeling (vaginale brachytherapie) met controle na de operatie, is er geen extra verzekering nodig voor dit onderzoek. Alle deelnemende ziekenhuizen hebben de gebruikelijke aansprakelijkheidsverzekeringen en klachtenprocedures zoals voor iedere medische behandeling.

Waar kan ik terecht met mijn vragen?
Mocht u verdere vragen hebben over deze studie dan kunt u die stellen aan uw behandelend radiotherapeut-oncoloog of gynaecoloog, of aan (naam en telefoonnummer locale coördinator). Landelijke contactpersonen voor deze studie zijn: Dr C.L. Creutzberg (radiotherapeut-oncoloog; tel 071-5265120) en Dr R.A. Nout (radiotherapeut-oncoloog; tel 071-5261990). Ook kunt u contact opnemen met een onafhankelijke arts: (naam en tel nr locale onaf arts), of met Prof. Dr A.J. Gelderblom, tel. 071-5263486). Deze artsen hebben geen direct belang bij dit onderzoek, maar zijn wel op de hoogte van de aard en inhoud ervan.
Verdere informatie kunt u ook vinden in folders van KWF Kankerbestrijding: “Baarmoederkanker”, “Radiotherapie”, “Chemotherapie” en “Onderzoek naar nieuwe behandelingen van kanker”. U krijgt deze folders van uw arts, of kunt ze aanvragen via www.kwfkankerbestrijding.nl
TOESTEMMINGSVERKLARING
voor deelname aan wetenschappelijk onderzoek

Titel van het onderzoek: “PORTEC-4, een onderzoek naar de waarde van inwendige bestraling en optimale dosis daarvan bij patiënten met baarmoederkanker (endometriumcarcinoom)”.

Ik ben naar tevredenheid over het onderzoek geïnformeerd. Ik heb de schriftelijke informatie goed gelezen. Ik ben in de gelegenheid geweest om vragen te stellen over het onderzoek. Mijn vragen zijn naar tevredenheid beantwoord. Ik heb goed over deelname aan het onderzoek kunnen nadenken. Ik heb het recht mijn toestemming op ieder moment weer in te trekken zonder dat ik daarvoor een reden hoef te geven.

Ik geef toestemming voor deelname aan het onderzoek. Ik geef hierbij ook toestemming voor deelname aan het kwaliteit van leven onderzoek.

Ik geef wel/geen* toestemming voor het onder code bewaren van een heel klein stukje van het tumorweefsel voor aanvullend wetenschappelijk onderzoek in de toekomst. * doorhalen wat niet van toepassing is

Naam en voorletters: ………………………………………………………………………………

Geboortedatum: ……………………………………………………………………………………

Handtekening: ………………………………………… Datum: ……………………………….

Ondergetekende verklaart dat de hierboven genoemde persoon zowel mondeling als schriftelijk over het bovenvermelde onderzoek is geïnformeerd Hij/zij verklaart tevens dat een voortijdige beëindiging van de deelname door bovengenoemde persoon van geen enkele invloed zal zijn op de zorg die haar toekomt.

Naam en voorletters: ………………………………………………………………………………

Functie: ……………………………………………………………………………………

Handtekening: ………………………………………… Datum: ……………………………….

Dit formulier is bestemd voor onderzoek met meerderjarigen die wilsbekwaam zijn. Bij dit soort onderzoek moet door de betrokkenen zelf toestemming worden verleend. Het origineel dient in het medisch dossier te worden bewaard.
## APPENDIX I. FORMS AND PROCEDURES FOR COLLECTING DATA

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

### Table for filling out forms

<table>
<thead>
<tr>
<th>Time after date of registration/randomization</th>
<th>Registration Completion of BT</th>
<th>End of treatment*</th>
<th>6-monthly until year 3</th>
<th>At year 4 and 5</th>
<th>At year 7 and 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>X</td>
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</tr>
<tr>
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<td>X</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>X                X     X     X (X)</td>
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<td></td>
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<td>6</td>
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<tr>
<td>7</td>
<td>X</td>
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<tr>
<td>8</td>
<td>X</td>
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<tr>
<td>QoL</td>
<td>X</td>
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</tr>
</tbody>
</table>

*3-4 weeks after completion of brachytherapy, or 6 weeks after randomisation in the observation group, respectively*
### APPENDIX J. Checklist for investigations at registration, treatment and follow-up

<table>
<thead>
<tr>
<th>Time after date of registration/randomization</th>
<th>Before Registration</th>
<th>2-3 wks after completion of BT</th>
<th>1st - 5th year: every 6 months</th>
<th>1st - 5th year: annually</th>
<th>5th - 7th year: annually</th>
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</thead>
<tbody>
<tr>
<td>Medical history</td>
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<tr>
<td>Physical and pelvic exam</td>
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<td>X</td>
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<tr>
<td>Vaginal atrophy scoring and measurements of length and width</td>
<td>At 1st BT session</td>
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<td></td>
</tr>
<tr>
<td>Tumor status</td>
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<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Performance status</td>
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<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Toxicity scoring</td>
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<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planning CT scan</td>
<td>At first brachytherapy</td>
<td>..... on indication .....</td>
<td>At completion of BT (resp 6 wks from randomization in the NAT arm) and at 6, 12, 18, 24, 36, and 60 months from randomization; these will be sent directly to the patient’s home address</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>