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Adjuvant treatment for endometrial cancer: efficacy, toxicity and quality of life

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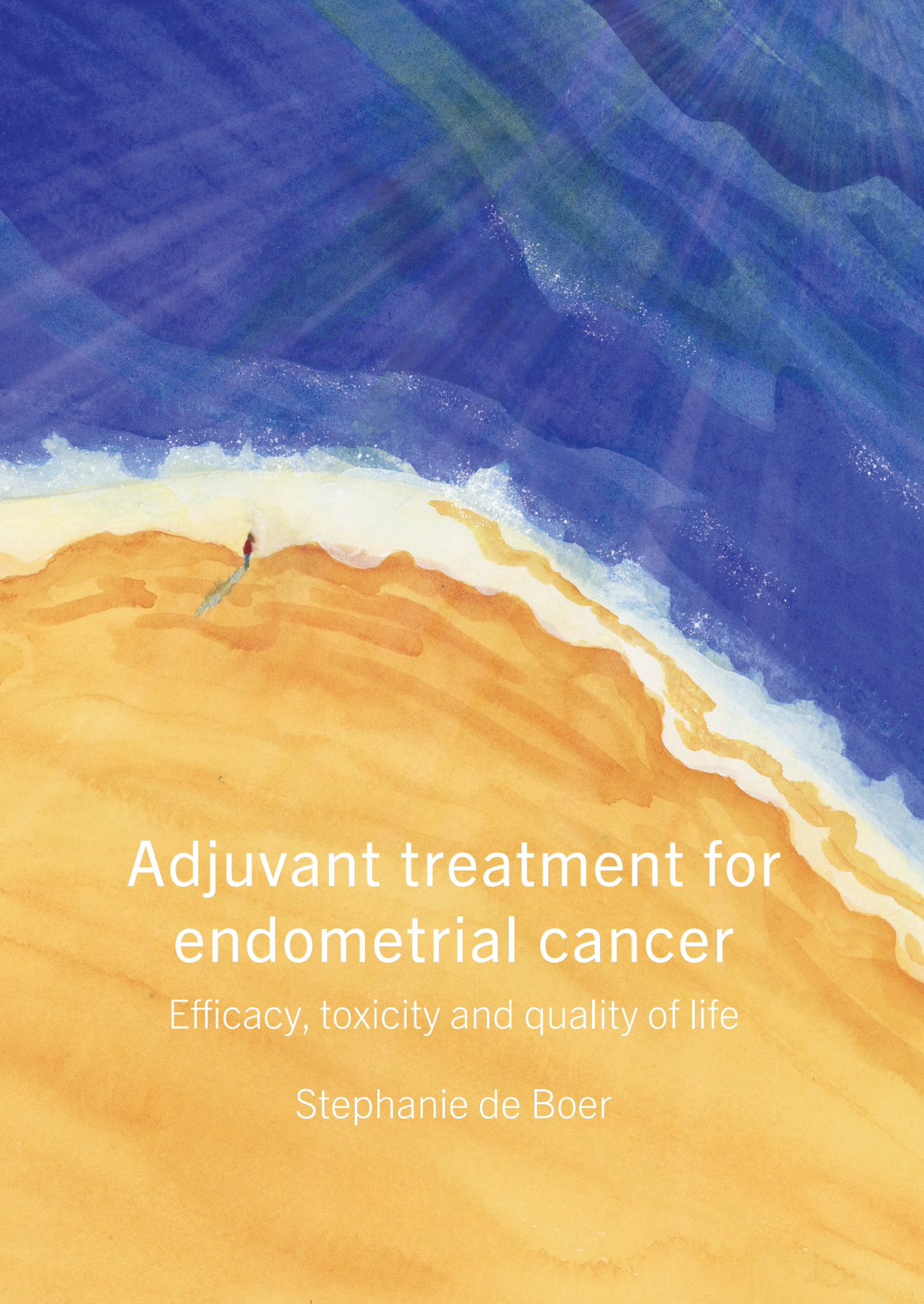

Adjuvant treatment for endometrial cancer

Efficacy, toxicity and quality of life

Stephanie de Boer

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Efficacy, toxicity and quality of life

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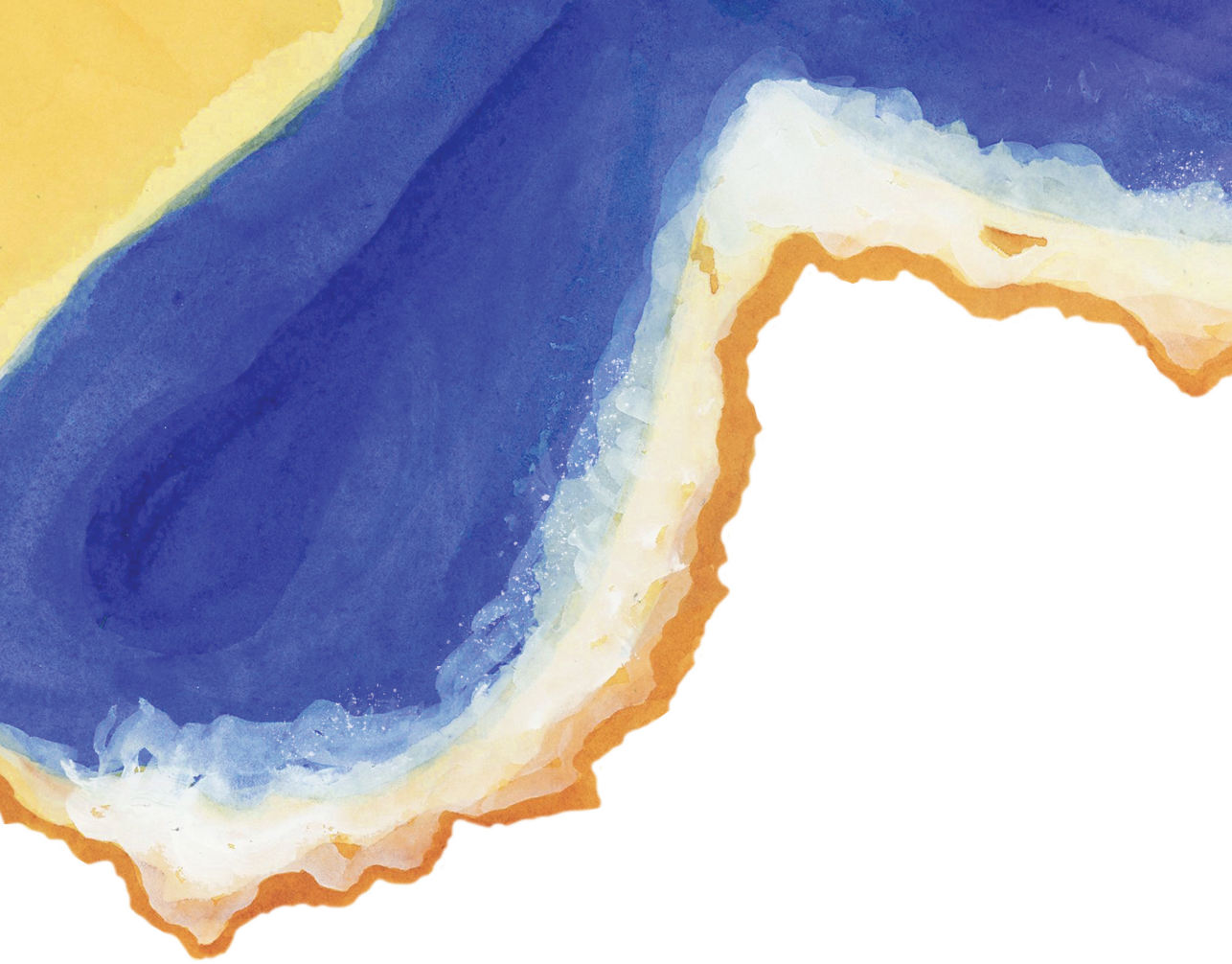

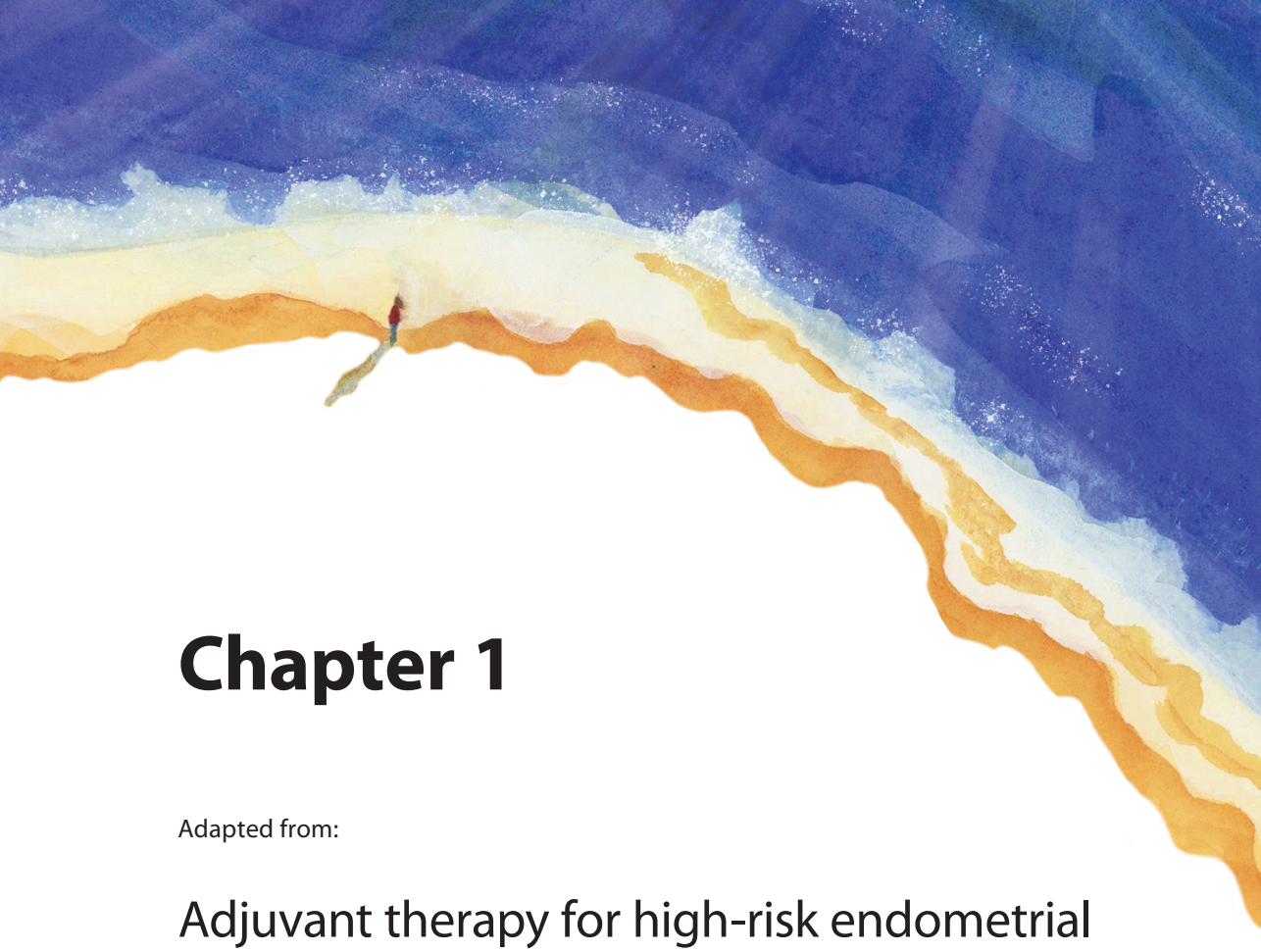

Chapter 1

Adapted from:

Adjuvant therapy for high-risk endometrial cancer: recent evidence and future directions

Stephanie M. de Boer, Remi A. Nout, Tjalling Bosse, Carien L. Creutzberg

Expert Review of Anticancer Therapy 2019 Jan;19(1):51-60

1. INTRODUCTION

1.1 Epidemiology of endometrial cancer

Endometrial cancer is the most common gynecological cancer in developed countries and primarily affects postmenopausal women between 60 and 85 years of age, with a median age at diagnosis of about 65–76 years. Women with endometrial cancer often have comorbidities such as cardiovascular diseases, diabetes, hypertension, and obesity. The incidence of endometrial cancer has been increasing in the past decades due to ageing of the population and increased rates of obesity. There is convincing evidence that greater body fatness, leading to elevated estrogen levels, is the most likely cause of the increased risk of endometrial cancer among obese women.[1-3] The estimated number of uterine cancers diagnosed in the Netherlands in 2017 is 2025, and the estimated number of endometrial cancer-related deaths is about 493, reflecting the fact that the majority of patients have a favorable prognosis (Figure 1).[4] This is largely because most women present with early-stage disease (confined to the uterus) due to early symptoms of vaginal bleeding.

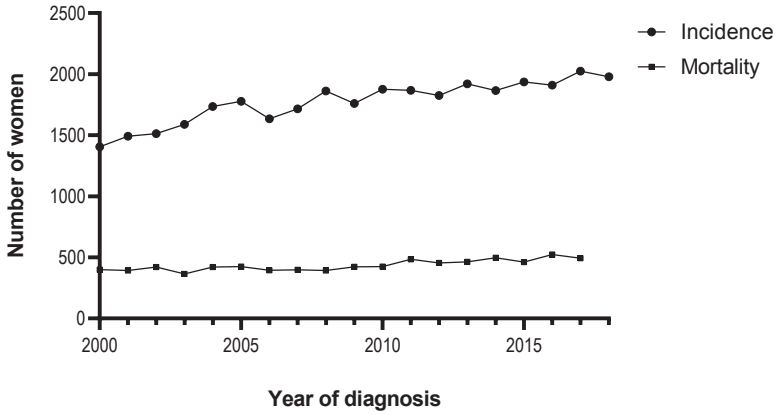

Figure 1. Netherlands Cancer Registry: incidence and mortality of endometrial cancer in the Netherlands between 2000 and 2018[4]

1.2 Surgery

Standard surgery for endometrial cancer consists of total abdominal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy (TAH/TLH + BSO). Laparoscopic surgery is to be preferred in early-stage tumours, as randomised trials showed no difference between abdominal or laparoscopic approaches in risk of complications, disease-free and overall survival. However, improved short-term quality of life, shorter hospital stay, less pain, and quicker resumption of daily activities were reported after the laparoscopic procedure.[5-9] There is considerable controversy whether a pelvic and/

or para-aortic lymphadenectomy should be performed. The main rationale for lymphadenectomy is comprehensive surgical staging, with triaging of patients for adjuvant therapy. Two large randomised trials have been published which found no difference in progression-free or overall survival rates when comparing surgery with and without lymphadenectomy in women with early stage endometrial cancer.[10,11]

Patients who undergo a pelvic and/or para-aortic lymphadenectomy are more likely to develop surgery-related toxicities, mainly lymphedema. A meta-analysis assessing 1922 patients reported a higher risk (RR 8.39) of lymphedema or symptomatic lymphocyst formation in patients who underwent a lymphadenectomy.[12] Several trials showed increasing rates of leg edema with increasing number of lymph nodes dissected, independent of the use and type of adjuvant therapy.[13,14]

As most of the trials cited above included a large majority of women with early stage, low-intermediate risk disease, there is still lack of evidence on the value of lymphadenectomy to direct adjuvant treatment in high-risk disease. The international STATEC trial was initiated to determine whether lymphadenectomy could reduce adjuvant treatment in node-negative women with similar survival. Women with stage I grade 3 endometrial cancer were randomised to surgery with or without lymphadenectomy. Unfortunately, the trial was recently closed early due to a low accrual rate.[15]

The sentinel node procedure has become part of standard surgery and has been proven safe to replace lymph node dissection in various tumour types such as breast cancer, melanoma, and vulvar cancer. Although some trials have reported on the sensitivity and specificity of the sentinel node procedure in endometrial cancer, sentinel lymph node evaluation in endometrial cancer is less straightforward than in breast cancer and vulvar cancer, where the sentinel node is usually represented by 1 or 2 nodes. In endometrial cancer, up to about eight sentinel nodes can be found bilaterally, most often in the iliac region but less frequently also at other sites, including the para-aortic region. Furthermore, in view of the low risk of disease spread in the majority of patients with early stage disease, the exact role of sentinel node procedure is still unknown.

First trials of the sentinel node procedure including ultrastaging have shown a high degree of diagnostic accuracy in detecting macroscopic and microscopic lymph node metastases. Detection of isolated tumour cells poses a new clinical challenge, as these are not considered true metastases in most tumour types. Sentinel node biopsy has the potential to fully replace lymphadenectomy (when indicated) and spare patients the associated morbidity of extensive lymph node dissection, especially lymphedema.[16-18]

1.3 Risk classification

There are well-defined clinicopathological risk factors for endometrial cancer and the indication for adjuvant treatment is determined on the basis of these factors (see also paragraph 1.5).

FIGO stage

Definitive staging according to the International Federation of Gynecology and Obstetrics (FIGO) staging system is based on surgical and pathology findings. The staging and histological classification systems for endometrial cancer have been updated in the past decades. The most recent FIGO staging was published in 2009, which replaced 1988 FIGO staging (Table 1).[19,20] This classification takes the extent of the tumour (confined to the uterus, cervix or local spread to serosa, adnexae, parametrium, vagina) into account, as well as pelvic and/or para-aortic and distant metastases. The new 2009 FIGO staging system for endometrial cancer is highly prognostic and survival declines with increasing stage: 89.6% for stage IA endometrial cancer compared with 49.4% for stage IIIC2 endometrial cancer.[21]

Table 1. FIGO 2009 staging of endometrial cancer[19,20]

Stage	Description
Stage I	Tumour confined to corpus uteri
IA	No or less than half myometrial invasion
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
IIIA	Tumor invades the serosa and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic nodes with or without positive pelvic nodes
Stage IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Invasion of bladder/bowel mucosa
IVB	Distant metastasis, including intra-abdominal metastases and/or inguinal lymph nodes

Histological type and grade

Traditional histological classification used to categorize endometrial cancer into two subgroups: endometrioid versus non-endometrioid cancers.[22] Endometrioid endometrial cancer is the most common subtype, and these are often estrogen-dependent tumours of low grade and typically occurring in relatively younger women (Figure 2).[23] Endometrioid endometrial cancers are graded according to FIGO classification based on the percentage of non-squamous solid growth and the degree of nuclear atypia.[23] Non-endometrioid tumours are often estrogen-independent, of high tumour grade, occur in older women, and have an unfavorable prognosis. These tumours include various histological subtypes such as serous and clear cell carcinomas, which are high grade by definition. Serous and clear cell cancers have a higher risk of aggressive intra-abdominal spread and a poorer prognosis.[24-26] However, when diagnosed at an early stage, similar

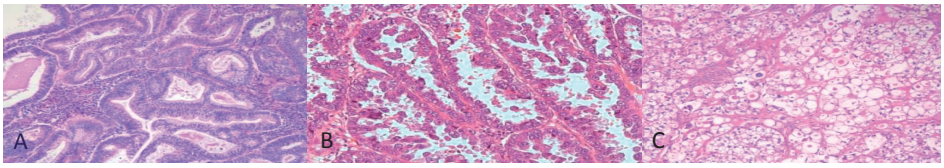

Figure 2. Hematoxyline-eosine (HE) coupes: endometrioid (A), serous (B) and clear cell (C) endometrial cancer

survival rates have been reported for serous and clear cell endometrial cancer as compared to grade 3 endometrioid endometrial cancers.[27]
Mixed epithelial and mesenchymal tumours and uterine sarcomas are rare cancers and are regarded as separate entities; these will not be discussed in this thesis.

Lymphovascular space invasion

Lymphovascular space invasion (LVSI) is defined as the presence of tumour cells in a space lined by endothelial cells outside the immediate invasive border.[28] LVSI is an independent prognostic factor for pelvic lymph node metastases, distant metastases, recurrence and survival, and is also prognostic for recurrence and survival in the absence of lymph node metastases.[29-31] Using a three-tiered scoring system, substantial LVSI (in contrast to focal or no LVSI) is the strongest independent prognostic factor.[28]

Age

Elderly women more often present with endometrial cancers of non-endometrioid histology with a poorer prognosis. Apart from this association, age has consistently been found to be an independent prognostic factor as well. Women with an age at diagnose of ≥60 have an increased risk for locoregional recurrence, distant metastases and endometrial cancer-related death.[32-36]

1.4 Pathology assessment

Reproducibility of the pathology diagnosis is essential, as adjuvant treatment is largely based on pathology criteria. Previous studies of pathology review by expert subspecialty pathologists, however, have shown that discrepancies with and without consequences for adjuvant treatment frequently occur. Evaluation of female reproductive tract pathology had the highest rates of discrepancies between original and review pathology assessment,[37] and a Canadian study reported endometrial cancer as the tumour site with most frequent differences in pathological assessment.[38]
Retrospective pathology review was performed in the PORTEC-1 and 2 trials, which showed that 24% and 14%, respectively, of patients were in retrospect ineligible for the trials, mainly based on shifts in tumour grading with low reproducibility of the intermediate grade.[32,39,40] It could therefore be considered to perform pathology review prior

to trial inclusion. However, upfront pathology review is time-consuming, expensive, and logistical procedures are complicated and might therefore not be part of standard procedure.

1.5. Adjuvant treatment

Low-intermediate risk endometrial cancer

As most (75–80%) patients with endometrial cancer present with early disease, risk factors have been defined by which those with stage I endometrial cancer are subdivided in low-risk, intermediate risk, and high-risk disease (Table 2). Adjuvant treatment for women with stage I endometrial cancer is based on the major risk factors histological type, histological grade, depth of myometrial invasion, age, and LVSI.[41]

Table 2. Risk groups of endometrial cancer according to GOG, PORTEC and ESMO-ESGO-ESTRO consensus

Risk group	GOG-99[43]	PORTEC[32]	ESMO-ESGO-ESTRO consensus[41]
Low	Stage I endometrioid, no invasion	Stage I endometrioid, grade 1-2, <50% invasion, any age	Stage I endometrioid, grade 1–2, <50% myometrial invasion, LVSI negative
Low-intermediate	Stage I endometrioid	Stage I endometrioid, grade 1-2, ≥50% invasion, age <60	Stage I endometrioid, grade 1–2, ≥50% myometrial invasion, LVSI negative
High-intermediate	Stage I endometrioid with risk factors (grade 3, ≥ 66% invasion, LVSI): age ≥ 70 with 1 risk factor, age ≥ 50 with 2 risk factors and any age with all risk factors.	Stage I endometrioid, grade 1-2, ≥50% invasion, age ≥60; Stage 1 endometrioid, grade 3, <50% invasion, age ≥60	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status. Stage I, endometrioid, grade 1–2, LVSI unequivocally positive, regardless of depth of invasion
High	Stage II-III endometrioid; Stage I-III non-endometrioid	Stage I endometrioid, grade 3, ≥50% invasion; Stage II-III endometrioid; Stage I-III non-endometrioid	Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status; Stage II; Stage III endometrioid, no residual disease; Non-endometrioid (serous or clear cell or undifferentiated carcinoma, or carcinosarcoma)
Advanced	Stage IV	Stage IV	Stage III residual disease and stage IVA
Metastatic	Stage IV	Stage IV	Stage IVB

Abbreviations: LVSI; lymph-vascular space invasion

Patients with low-risk disease, about 50% of all endometrial cancer cases, are those with stage I endometrioid type endometrial cancer, grade 1–2, with less than 50% myometrial invasion, and without LVSI (Table 2). These women have a very favorable outcome with surgery alone (95% recurrence-free survival at 5 years) and adjuvant therapy is therefore not indicated. Several large randomised trials have shown that for patients with (high-)

intermediate risk endometrial cancer, adjuvant radiotherapy significantly reduces the risk of vaginal and pelvic recurrence, but without overall survival benefit (Table 3).[32,42-45] In the PORTEC-1 trial, the majority of locoregional recurrences (75%) were located in the vaginal vault, and most could be cured with radiotherapy at the time of recurrence, with 73% and 65% 3- and 5-year survival after recurrence.[46] After publication of the PORTEC-1 and GOG-99 trials, the indication for radiotherapy became limited to women with high-intermediate risk factors, as these had about 20% locoregional recurrence with surgery alone, which was reduced to 5% with adjuvant external beam radiotherapy (EBRT).[39] Subsequently, the PORTEC-2 trial was initiated to investigate the role of vaginal brachytherapy as compared to EBRT for women with high-intermediate risk endometrial cancer. PORTEC-2 showed high efficacy of vaginal brachytherapy in reducing vaginal recurrence of endometrial cancer, with similarly high 5-year vaginal control rates in both arms (98%). As fewer side effects and better health-related quality of life were reported with vaginal brachytherapy as compared to EBRT, vaginal brachytherapy became the standard adjuvant treatment for women with high-intermediate risk endometrial cancer.[40,47]

High-risk endometrial cancer

About 15–20% of all women with endometrial cancer are diagnosed with high-risk endometrial cancer, which comprises endometrioid endometrial cancer (EEC) stage I, grade 3 with outer 50% myometrial invasion and/or with LVSI; stage II or III EEC; or stage I-III with non-endometrioid (serous or clear cell) histologies (Figure 2). Higher incidence of distant metastases and endometrial cancer-related death have been reported for women with high-risk endometrial cancer.[28,48-50]

Pelvic external beam radiation therapy (EBRT) has been standard adjuvant treatment for women with high-risk endometrial cancer for many decades, although there is a paucity of evidence on improvement of survival. Randomised trials have compared adjuvant chemotherapy alone with pelvic EBRT alone.[33-35] A Japanese trial[34] randomised 385 patients with stage IC-III endometrial cancer to adjuvant EBRT or three cycles of cyclophosphamide 333mg/m2, doxorubicin 40mg/m2 and cisplatin 50mg/m2 (CAP) chemotherapy every 4 weeks. No significant differences in progression-free and overall survival were observed. Five-year overall survival rates were high in both treatment arms, 85% (EBRT) vs. 87% (CAP), reflecting that approximately 60% of patients had stage IC disease and 85% had grade 1–2 tumours. It was suggested in an unplanned subgroup analysis that women with high-risk factors (n = 120) defined as stage IC patients with either age over 70 or with grade 3 endometrioid adenocarcinoma or stage II/IIIA (positive cytology) disease, might have benefited from chemotherapy, but this was not found for stage III disease.

Table 3. prospective phase III trials investigating adjuvant radiotherapy in intermediate risk endometrial cancer

Trial	Enrolment	No. of patients	Surgery	Eligibility	Randomisation	Locoregional recurrence	Survival
Aalders et al[44]	1968-1974	540	TAH-BSO	Stage I	VBT vs VBT + EBRT	5 yrs: 7% vs 2% (p<0.01)	5 yrs: 89% vs 91% (p=NS)
Creutzberg et al (PORTEC-1)[32]	1990-1997	714	TAH-BSO	Stage IB G2-3; stage IC G1-2	EBRT vs NAT	5 yrs: 14% vs 4% (p<0.001)	5 yrs: 85% vs 81% (p=0.31)
Keys et al (GOG-99)[43]	1987-1995	392	TAH-BSO + LND	Stage IB/C; stage II (occult)	EBRT vs NAT	2 yrs: 12% vs 3% (p=0.007)	4 yrs: 86% vs 92% (p=0.557)
Blake et al (ASTEC/EN.5)[42]	1996-2005	905	TAH-BSO +/- LND	Stage IA/B G3; IC; stage II; serous/CC	EBRT vs NAT	5 yrs: 6 vs 3% (p=0.02)	5 yrs: 84% vs 84% (p=0.98)
Nout et al (PORTEC-2)[40]	2002-2006	427	TAH-BSO	Age > 60 and stage IB G3 or stage IC G1-2; stage IIA	EBRT vs VBT	5 yrs: 5% vs 2% (p=0.17)	5 yrs: 85% vs 80% (p=0.57)
Sorbe at al[45]	1997-2008	527	TAH-BSO	Stage I intermediate risk	VBT vs VBT + EBRT	5 yrs: 5% vs 1.5% (p=0.013)	5 yrs: 90% vs 89% (p=0.55)

Abbreviations: TAH-BSO, total abdominal hysterectomy with bilateral salpingo-oophorectomy; LND, lymph node dissection; EBRT, external beam radiotherapy; VBT, vaginal brachytherapy; NAT, no additional treatment; CC, clear cell; G, grade.

In an Italian trial[33], 345 patients with high-risk endometrial cancer were randomised to EBRT or five cycles of cyclophosphamide 600 mg/m2, doxorubicin 45 mg/m2 and cisplatin 50mg/m2 (CAP) chemotherapy every 4 weeks. Sixty-five percent of patients had stage III disease and 56% of patients had a grade 3 endometrioid tumour. EBRT delayed pelvic recurrence and chemotherapy delayed distant metastases, but no differences in overall and progression-free survival were found: 5-year overall survival was 69% (EBRT) vs. 66% (CAP) and 5- year progression-free survival was 63% vs. 63%. In these two trials, only women with endometrioid tumours were included.

In the GOG-122 trial[35], patients with advanced stage disease (stage III and IV endometrial cancer, residual macroscopic disease ≤2 cm allowed) were randomised to receive whole-abdominal irradiation (WAI) or chemotherapy (eight cycles of doxorubicin 60mg/m2 and cisplatin 50 mg/m2). Chemotherapy significantly improved overall survival (55% vs. 42%). However, event rates were similar (54 vs. 50%) and 5- year rates of pelvic recurrence were 18% for chemotherapy and 13% for RT. Substantial grade 3–4 toxicity occurred in patients treated with chemotherapy, and significantly higher rates of peripheral neuropathy were reported after treatment by patients treated with chemotherapy.[51]

Relatively large multicenter and single center retrospective studies reported higher rates of pelvic recurrence if high-risk patients were treated without radiotherapy supporting the continued use of locoregional radiotherapy in patients undergoing adjuvant chemotherapy.[52-54] In a phase II trial (RTOG 9708) among women with high-risk endometrial cancer, the combination of EBRT with two concurrent cycles of cisplatin 50 mg/m2 on days 1 and 28, followed by four adjuvant cycles of cisplatin 50 mg/m2 and paclitaxel 175 mg/m2 was tested in 46 patients, resulting in favourable 4-year overall and disease-free survival rates of 85% and 81%, respectively.[55] A completion rate of 98% was reported. Acute grade 3 and grade 4 adverse events were reported in 12 (27%) and 1 (2%) patient during concurrent chemotherapy, respectively, and in 9 (21%) and 26 (62%) patients during adjuvant chemotherapy. Chronic grade 3 and 4 adverse events were reported in 7 patients (16%) and 1 patient (2%).[56]

1.6 Toxicity and health-related quality of life

Although endometrial cancer primarily affects older, postmenopausal women with frequent comorbidities, the prognosis for the majority of endometrial cancer patients is good. It is therefore important to weigh the benefits in terms of overall or progression-free survival benefit against the costs in terms of toxicity, treatment duration and both short-term and long-term health-related quality of life. There is only limited agreement between patient and physician reported scoring of toxicities, with significant physician under-reporting of lower grade toxicities, which represent symptoms with impact on the patients' daily lives.[57,58] Patient-reported health-related quality of life (HRQOL) analy-

sis is therefore important to evaluate long-term symptoms and their burden in addition to physician-reported adverse events.

For women treated with pelvic EBRT in the PORTEC-1 and 2 trials increased rates of acute toxicities, mainly gastro-intestinal, have been reported.[47,59] In the PORTEC-1 with EBRT there was a small risk (3%) of severe (grade 3) gastro-intestinal complications (requiring surgery), and a substantial risk (22%) of mild side effects. Although 50% of these acute effects were transient, women with acute RT related toxicity had an increased risk of late radiotherapy complications. In the PORTEC-1 trial late radiotherapy complications were related to the radiation techniques used, with higher rates of late complications in women treated with parallel opposing fields compared with multiple field techniques.[59]

For evaluation of radiotherapy related toxicities the long-term quality of life is relevant as it is known that the bladder is a late-responding organ.[60,61] Long-term HRQOL analysis of the PORTEC-1 trial showed that even after 10-15 years, bowel and urinary symptoms were more frequent among women treated with EBRT compared to the control group without adjuvant treatment, leading to lower physical and role-physical functioning in the EBRT group.[62]

In the PORTEC-2 trial, women treated with EBRT reported slightly more bowel symptoms, especially diarrhea (difference of 7 points on EORTC QLQ-c30 scale) and fecal leakage (5 points difference), leading to related limitations in daily activities with lower social functioning, 5 years after treatment.[47] Women treated with vaginal brachytherapy reported a better HRQOL, similar to that of a norm population matched for age and sex.

Quality of life data evaluating on toxicities caused by the addition of chemotherapy to pelvic EBRT in women with endometrial cancer is limited. Data regarding toxicity and health-related quality of life of women treated with carboplatin and paclitaxel chemotherapy are mainly available from first-line therapy in ovarian cancer trials. Despite the different tumour type, comparison is relevant as women with ovarian cancer are of similar age and also underwent pelvic surgery. From the ovarian cancer trials with a 3-weekly schedule of carboplatin and paclitaxel it is known that moderate to severe haematological and non-haematological toxic effects including sensory and motor neuropathy are common adverse events.[63,64]

1.7 Aims and outline of this thesis

The PORTEC-3 trial was initiated to investigate the benefit in overall and failure free survival of combined adjuvant chemotherapy and radiotherapy for women with high-risk endometrial cancer, and determine the added toxicities and impact on quality of life of this treatment combination compared to radiotherapy alone. The outcomes of this trial are discussed in the following chapters of this thesis.

The aims of this thesis were:

1. To evaluate long-term health-related quality of life after external beam radiotherapy compared with vaginal brachytherapy among PORTEC-2 trial participants, evaluate long-term bowel and bladder symptoms, and assess the impact of cancer diagnosis and treatment on these endometrial cancer survivors.
2. To investigate the value and clinical consequences of upfront pathology review for high-risk endometrial cancer with respect to eligibility and inter-observer variation.
3. To evaluate the impact of combined adjuvant chemotherapy and radiation therapy on short-term and long-term toxicity and patient-reported health-related quality of life compared with radiotherapy alone.
4. To evaluate the role of combined adjuvant chemotherapy and radiotherapy in women with high-risk endometrial cancer in terms of overall and failure free survival in the PORTEC-3 trial.

Chapter 2 describes the long-term quality of life and impact of diagnosis and treatment on long-term endometrial cancer survivors treated in the PORTEC-2 trial, which compared adjuvant EBRT with vaginal brachytherapy in women with high-intermediate risk endometrial cancer.
In the PORTEC-3 trial, upfront pathology review by an expert gynaeco-pathologist was mandatory to confirm eligibility for the trial. In **chapter 3** the value of this upfront pathology review is described, focusing on the proportion of women who were ineligible for the PORTEC-3 trial after pathology review and the inter-observer variability between original and review pathology assessments. In **chapter 4** the results of the 2-year adverse events and patient reported health-related quality of life analysis in women treated in both arms of the PORTEC-3 trial are compared and put into perspective. In **chapter 5** the final results of the PORTEC-3 trial are presented, including overall survival, failure-free survival and toxicity outcomes with a median follow up of 60 months. **Chapter 6** describes a more detailed analysis of the patterns of recurrence and updated survival outcomes of the PORTEC-3 trial, with a median follow up of 72 months. **Chapter 7** provides a summary and a general discussion of the data presented in this thesis, focusing on implications for clinical practice and future perspectives.

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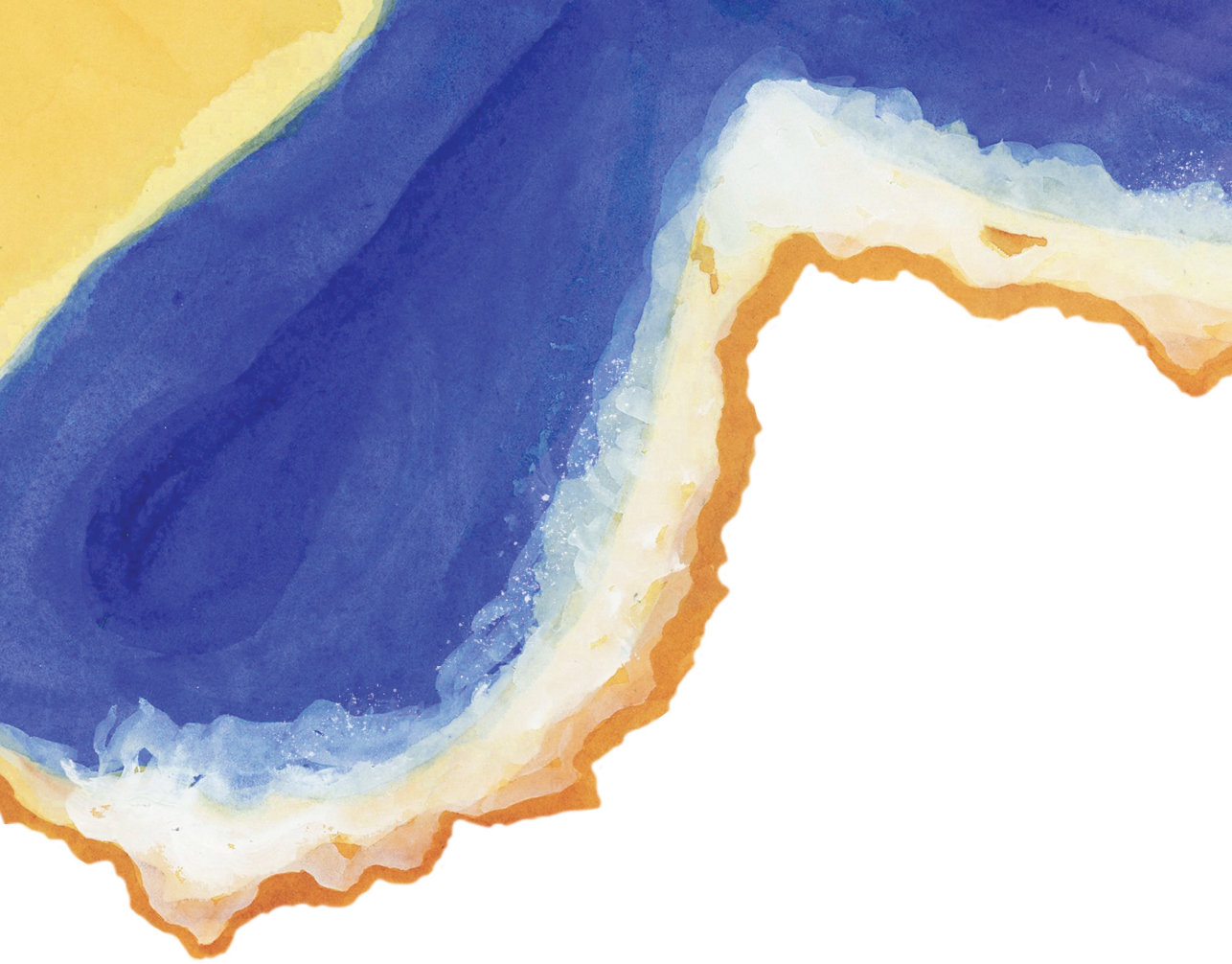

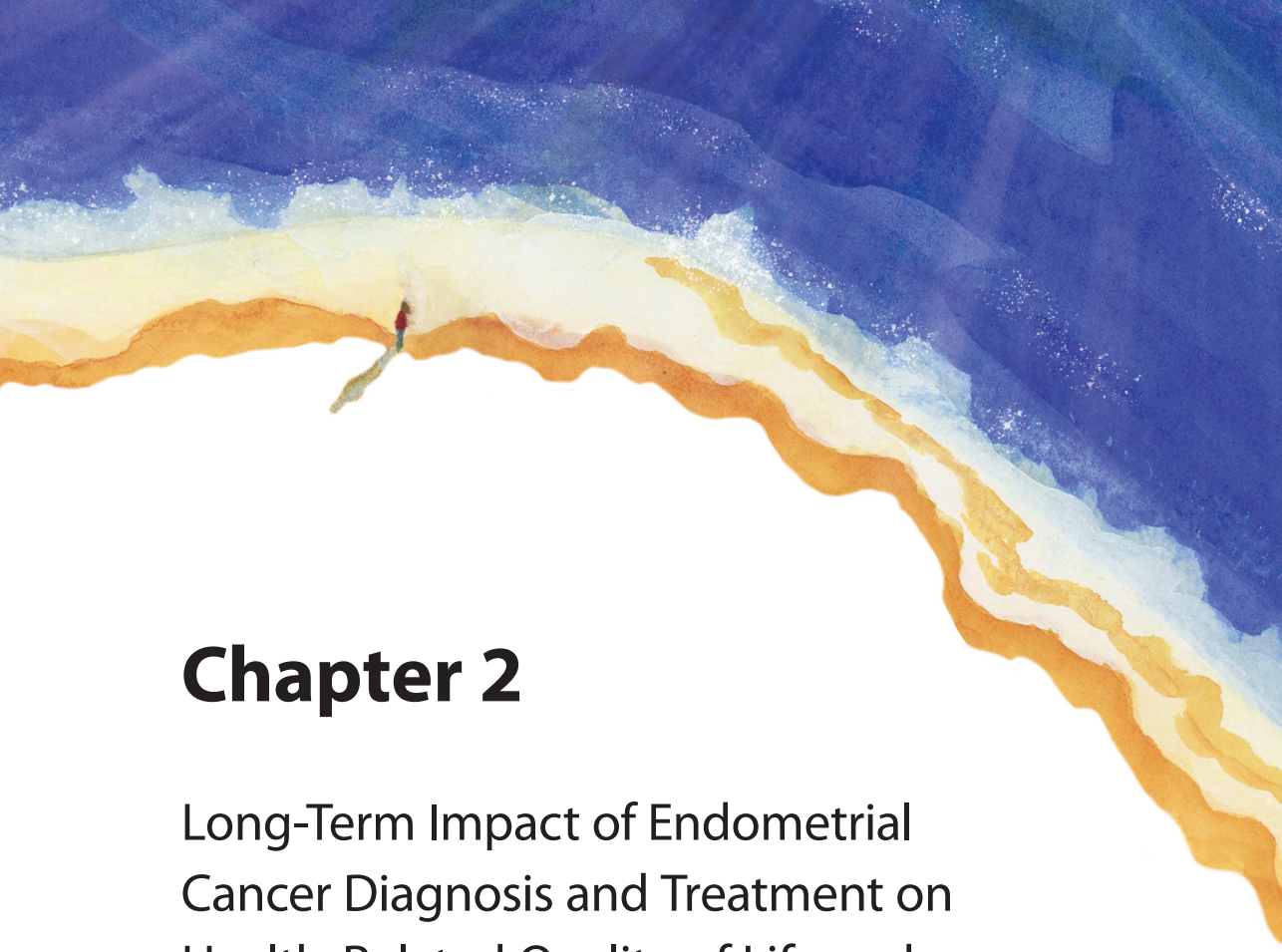

Chapter 2

Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomised PORTEC-2 Trial

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ABSTRACT

Purpose

To evaluate the long-term health-related quality of life (HRQL) after external beam radiation therapy (EBRT) or vaginal brachytherapy (VBT) among PORTEC-2 trial patients, evaluate long-term bowel and bladder symptoms, and assess the impact of cancer on these endometrial cancer (EC) survivors.

Patients and Methods

In the PORTEC-2 trial, 427 patients with stage I high-intermediate-risk EC were randomly allocated to EBRT or VBT. The 7- and 10-year HRQL questionnaires consisted of EORTC QLQ-C30; subscales for bowel and bladder symptoms; the Impact of Cancer Questionnaire; and 14 questions on comorbidities, walking aids, and incontinence pads. Analysis was done using linear mixed models for subscales and (ordinal) logistic regression with random effects for single items. A two-sided P value <.01 was considered statistically significant.

Results

Longitudinal HRQL analysis showed persisting higher rates of bowel symptoms with EBRT, without significant differences in global health or any of the functioning scales. At 7 years, clinically relevant fecal leakage was reported by 10.6% in the EBRT group, versus 1.8% for VBT (P=.03), diarrhea by 8.4% versus 0.9% (P=.04), limitations due to bowel symptoms by 10.5% versus 1.8% (P=.001), and bowel urgency by 23.3% versus 6.6% (P<.001). Urinary urgency was reported by 39.3% of EBRT patients, 25.5% for VBT, P=.05. No difference in sexual activity was seen between treatment arms. Long-term impact of cancer scores was higher among the patients who had an EC recurrence or second cancer.

Conclusions

More than 7 years after treatment, EBRT patients reported more bowel symptoms with impact on daily activities, and a trend for more urinary symptoms, without impact on overall quality of life or difference in cancer survivorship issues.

INTRODUCTION

Randomised trials have shown that pelvic external beam radiation therapy (EBRT) significantly reduced locoregional relapse compared with observation after surgery, but without survival benefit, and at the cost of mainly gastrointestinal adverse events.[1-5] The Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-2 trial showed that vaginal brachytherapy (VBT) was highly effective as compared with EBRT, with 2% vaginal recurrence at 5 years in both arms, and similar rates of locoregional relapse and overall survival.[6] Health-related quality of life (HRQL) analysis among PORTEC-2 trial patients at 5 years showed that women treated with VBT reported significantly fewer bowel symptoms, without limitations in daily activities, and higher social functioning scores than those who underwent EBRT. Symptom ratings of VBT patients remained similar to that of an age-matched normal population. Sexual functioning scores were lower in both groups compared with the age-matched population.[7] On the basis of these results VBT became the standard adjuvant treatment for patients with high-intermediate-risk endometrial cancer (EC).

Analysis of long-term HRQL in the previous PORTEC-1 trial, in which patients were randomised to EBRT or observation after surgery, showed that even after 10 to 15 years, bowel symptoms were still more frequent among patients who underwent EBRT. Urinary symptoms had become more frequent over time in both groups, but more clearly so among EBRT patients, with a significantly increased use of incontinence pads ("day and night usage" 42.9% vs 15.2% and "never use" 39% vs 60% for EBRT vs VBT, P<.001).[4, 8] For radiation therapy-related toxicity it is known that the bladder is a late-responding organ.[9, 10]

Little is known about the long-term impact of diagnosis and treatment on survivors of EC. The Impact Of Cancer (IOC) scale is a questionnaire measuring the positive and negative impact of cancer experience among long-term survivors.[11] Translation and validation of the IOC for use in The Netherlands have been reported.[12] The IOC version 2 (IOCv2) had similar impact domains in the Dutch sample, providing evidence that IOCv2 measured common and important survivor concerns across two different Western nations.

The present analysis was done to evaluate long-term HRQL after EBRT or VBT among PORTEC-2 trial patients, evaluate long-term bowel and bladder symptoms, and assess the impact of cancer on these EC survivors.

PATIENTS AND METHODS

Patient selection and study design of the PORTEC-2 trial

Between 2002 and 2006, 427 patients with stage I high-intermediate-risk EC who participated in the PORTEC-2 trial were randomised to EBRT or VBT. Details on patient selection, treatment, and HRQL have been described in previous publications.[6, 13] Baseline questionnaires and at least 1 follow-up questionnaire were received from 348 of 427 patients (81% of responders). Almost all patients had multiple follow-up questionnaires.[7] For the present analysis, patients were considered eligible if they were previous responders and were alive and disease-free according to the trial database.

HRQL assessment

Cancer-specific general HRQL was measured with the EORTC (European Organization for Research and Treatment of Cancer) Core questionnaire (QLQ-C30 v3.0).[14] Because the EC-specific EN24 module was not yet available, subscales from EORTC modules were combined into a bowel, bladder, and sexual symptom module.[15, 16] Likert-type response scales were used with a 4-point response scale, except for items 29 and 30 of the EORTC QLQ-C30 (7-point scale). All subscales and item responses were converted to 0 to 100 scales. Higher scores for functioning items and global quality of life scale represent a better level of functioning. For the symptom items, a higher score reflects a higher level of symptoms.

The HRQL questionnaire had been sent to the trial patients at 6-months intervals in the first 2 years and annually until 5 years. The 7- and 10-year questionnaires were supplemented with the IOCv2 and 14 extra questions on general health, comorbidities, and use of (walking) aids and incontinence pads.

The most recent scaling of the IOC questionnaire yielded the 37-item IOCv2, divided into 4 positive subscales and 4 negative subscales.[17] Respondents indicated their level of agreement from 1 (strongly disagree) to 5 (strongly agree). The PORTEC-1 trial patients had completed the IOCv1, which has 7 items less than IOCv2. An algorithm by Crespi et al[18] was used to impute these missing IOCv2 items for the PORTEC-1 patients for comparison. In view of overlapping questions, the IOCv1 question "ongoing cancer-related or treatment-related symptoms interfere with my life" was not asked. Therefore, the subscale "life interferences" was not computed. As a consequence, the overall scale "negative impact domains" consisted of 3 instead of 4 subscales.

Statistical methods

All statistical analyses were performed with SPSS version 20.0. The χ^2 test or Fisher exact test for categorical variables and t test for continuous variables were used to compare patient and tumour characteristics and to compare mean scores of symptoms at single

time points (P<.05 considered significant). Because of ongoing follow up, the 10-year results were only used for longitudinal analysis.

Analysis of HRQL was done according to EORTC Quality of Life Group guidelines. Baseline scores were compared with a t test, or Armitage trend test for single items. To obtain estimates of the EORTC QLQ-C30 and subscales at each of the fixed time points, a linear mixed model was used with patient as random effect and time (categorical), random assignment, and their interaction as fixed effects. Single items were analyzed using (ordinal) logistic regression with random effects. Differences in HRQL between the two treatment groups were tested by the Wald test in the linear or ordinal logistic mixed model (P random assignment), which excluded the baseline value.

The same test was applied to analyze significant changes of QOL scores over time (P-time), and score changes over time were compared between treatment groups (P-time by random assignment), which included the baseline value. To guard against false-positive results because of multiple testing, a 2-sided P value ≤.01 was considered statistically significant.

Guidelines on the interpretation of clinically relevant changes of EORTC QLQ-C30 scores were applied[19, 20]. Scales not included in the guideline were evaluated according to Osoba et al[21], who reported that patients valued a change of 5 to 10 as "little," 10-20 as "moderate," and more than 20 as "very much" difference.

The IOC scores were compared with a t test. Analysis of covariance was done to evaluate whether patient-related factors influenced scores between PORTEC-1 and PORTEC-2 patients.

RESULTS

HRQL population and compliance

Questionnaires were sent to 265 eligible patients with correct current address at the time points 7 years and 10 years from date of randomization. Response rate at 7 years was 205 of 265 (77%). Three patients only answered the comment page and were therefore not evaluable. One hundred nineteen patients had reached the 10-year time point, of whom 80 (67%) returned the questionnaire (Figure 1).

Of the 282 evaluable questionnaires (202 7-year and 80 10-year questionnaires), 76.2% had completed all items of the QLQ-C30, with rates of completion for the bladder and bowel items of 90.8% and 93.97%, respectively, and 69.8% for sexuality items. Among the responders who indicated to be sexually active (n=45), 86.7% had completed the sexual symptom subscale.

In the "remarks" section, 7 patients (2 EBRT, 5 VBT, of whom 1 only at 10 years) noted having been diagnosed with a second cancer in the pelvic region or an EC recurrence.

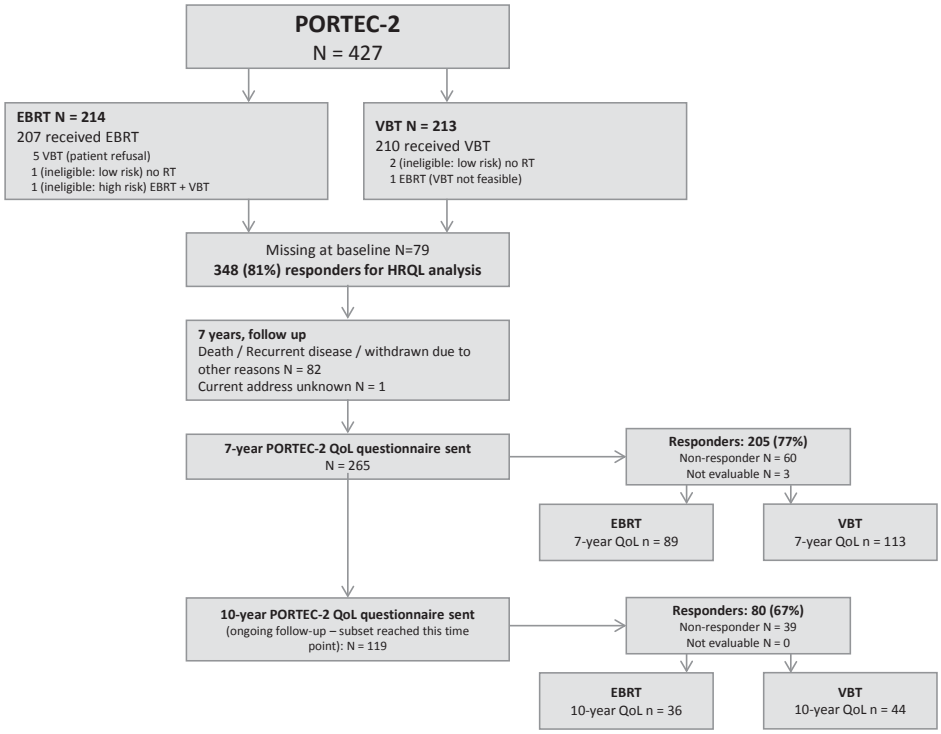

Figure 1. Consort diagram

Because this was not yet known in the trial database, this information was verified and proved correct in all cases. A second cancer outside the pelvic region was reported by another 5 patients. To avoid analysis of symptoms that could have been caused by a second cancer or recurrence, patients with an EC recurrence or a second cancer in the pelvic region were excluded for longitudinal and symptom analysis. The patients with an EC recurrence or a second malignancy (n=12) were analyzed separately for the IOC items.

General functioning

Table 1 shows the patient characteristics, both of the current participants and for the complete PORTEC-2 trial population. Responders at 7 years were slightly younger and had fewer comorbidities compared with the whole PORTEC-2 cohort; no other significant differences were found.

Scores on the QLQ-C30 functioning and global health scales did not significantly differ between the 2 treatment groups (Figure 2, Table 2). Although the overall longitudinal analysis found higher social functioning scores in the VBT group (P=.04), these higher scores were observed in the first 2 years after treatment, and similar thereafter. Sexual

activity was reported by only 19.4% of the patients, sexual interest by 28.1%. No difference in sexual interest and sexual activity was seen between treatment arms. Among patients who were sexually active, 87% (n=20) of EBRT patients reported sex to be enjoyable, compared with 50% (n=15) of VBT patients (P=.001). Symptoms ratings of vaginal dryness, shortening, or pain were not significantly different between the treatment arms.

Table 1. Patient characteristics of patients at 7 years compared to all PORTEC-2 patients

	Responders and evaluable at 7 years (n = 202)					**All patients PORTEC-2 (n=427)**				
	EBRT (n = 89)		**VBT (n = 113)**			**EBRT (n = 214)**		**VBT (n = 213)**		
	No. of patients	**%**	**No. of patients**	**%**	**p-Value[1]**	**No. of patients**	**%**	**No. of patients**	**%**	**p-Value[2]**
Age at randomisation, years										
Mean	67.1		68.1		0.28	69.3		69.8		**0.001**
Range	51-84		46-85			51-89		46-85		
< 60 years	6	6.7%	4	3.5%		8	3.7%	8	3.8%	
≥ 60 years	83	93.3%	109	96.5%		206	96.3%	205	96.2%	
Figo-stage (1988)[#]					0.94					0.81
IB	5	5.6%	6	5.3%		19	8.9%	16	7.5%	
IC	77	86.5%	98	86.7%		172	80.4%	171	80.3%	
IIA	7	7.9%	9	8.0%		23	10.7%	26	12.2%	
Histologic grade					0.55					0.74
Grade 1	39	43.8%	56	49.6%		99	46.3%	103	48.4%	
Grade 2	45	50.6%	50	44.2%		97	44.1%	94	44.1%	
Grade 3	5	5.6%	7	6.2%		18	8.4%	16	7.5%	
WHO performance					0.83					0.32
0	64	71.9%	87	77.0%		157	73.4%	141	66.5%	
1	25	28.1%	22	19.5%		56	26.2%	66	31.1%	
≥2	0	0.0%	4	3.5%		1	0.5%	5	2.4%	
Comorbidity										
IBS	1	1.1%	0	0.0%	0.32	4	1.9%	2	0.9%	0.23
Diabetes	6	6.7%	16	14.2%	0.08	28	13.1%	34	16.0%	0.19
Hypertension	32	36.0%	40	35.4%	0.94	75	35.2%	75	35.5%	0.95
Cardiovascular	16	18.2%	20	17.7%	0.93	47	22.2%	51	24.1%	0.13
Other	10	11.2%	9	8.0%	0.43	33	15.4%	33	15.6%	**0.02**

Abbreviations: EBRT, external beam radiation therapy; VBT, vaginal brachytherapy; WHO, World Health Organisation performance score; IBS, irritable bowel syndrome

[#]FIGO, International Federation of Gynaecology and Obstetrics (1988 staging criteria)

[1] p-value for comparison EBRT versus VBT of responders and evaluable at 7 years.

[2] p-value for comparison responders and evaluable at 7 years (present analysis) versus the initial PORTEC-2 cohort.

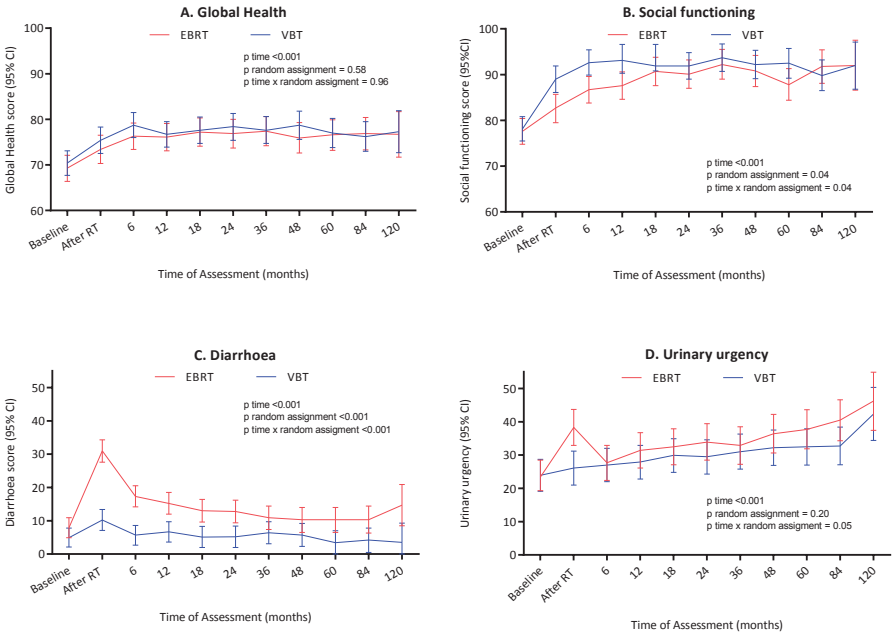

Figure 2. Patient functioning subscales and single-item symptom scores on the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and prostate cancer questionnaire module (EORTC PR-25). For (A) (Global Health score) and (B) (Social functioning score), a higher score indicates a higher level of functioning or activity. For (C) (Diarrhea) and D (Urinary urgency), a higher score indicates a higher level of symptoms. Abbreviations: EBRT = external beam radiation therapy; RT = radiation therapy; VBT = vaginal brachytherapy.

Bowel and bladder symptoms

Longitudinal analysis throughout the 10-year HRQL follow-up period showed higher rates of diarrhea, fecal leakage, and limitations in daily activities due to bowel symptoms in the EBRT group as compared with VBT (all P<.001; Table 2), similar to previous analyses.[8] At 7 years, significant and clinically relevant differences between EBRT and VBT patients were found for all bowel symptoms except for rectal blood loss, flatulence, and bowel cramps (Figure 3, Table 3). Moderate or severe symptoms of fecal leakage were reported by 10.6% versus 1.8% of EBRT versus VBT patients (P=.03), and moderate or severe diarrhea by 8.4% versus 0.9% (P=.037). Limitations in daily activities due to bowel symptoms were reported by 10.5% versus 1.8% (P=.001) and bowel urgency by 23.3% versus 6.6% (P<.001).

No differences were found in use of incontinence pads for fecal soiling (10.6% vs 8.1% for EBRT vs VBT). Fifty percent of patients who reported limitations in daily functioning due to bowel symptoms or fecal leakage used incontinence pads.

Table 2. Mean scores of QLQ-C30 functioning scales and symptom ratings by treatment arm

		Questionnaire time points			p-value		
			Months		Time	Randomization	Time by randomization
		Baseline	84	120			
EORTC QLQ-C30							
Global health	EBRT	69.3	76.9	76.7	**<0.001**	0.58	0.96
	VBT	70.4	76.2	77.3			
Functioning scales							
Social functioning	EBRT	77.6	91.8	92.0	**<0.001**	0.04	0.04
	VBT	78.1	89.8	92.0			
Cognitive functioning	EBRT	84.3	86.5	84.7	0.35	0.30	0.60
	VBT	86.7	85.5	86.7			
Emotional functioning	EBRT	75.6	82.9	83.7	**<0.001**	0.33	0.71
	VBT	76.3	84.7	87.5			
Physical functioning	EBRT	72.0	74.9	68.4	**<0.001**	0.34	0.75
	VBT	73.7	73.3	69.2			
Role functioning	EBRT	61.0	80.3	71.2	**<0.001**	0.34	0.15
	VBT	59.1	76.9	77.5			
QLQ C-30 symptom scoring							
Fatigue	EBRT	34.8	25.6	25.0	**<0.001**	0.14	0.37
	VBT	34.1	26.2	25.6			
Nausea and vomiting	EBRT	4.6	2.8	3.9	**<0.001**	0.04	0.34
	VBT	5.0	2.4	3.7			
Pain	EBRT	18.5	14.2	22.1	**<0.001**	0.33	0.46
	VBT	19.4	17.0	15.1			
Dyspnoea	EBRT	13.0	18.6	21.8	**<0.001**	0.53	0.05
	VBT	11.6	14.6	19.6			
Insomnia	EBRT	27.4	20.2	29.6	**0.003**	0.17	0.58
	VBT	25.9	23.3	21.5			
Appetite loss	EBRT	13.7	8.6	8.8	**<0.001**	0.03	0.02
	VBT	10.6	8.2	4.3			
Constipation	EBRT	13.4	8.3	5.7	**<0.001**	0.56	0.79
	VBT	12.9	7.4	9.1			
Diarrhoea	EBRT	7.9	10.3	14.7	**<0.001**	**<0.001**	**<0.001**
	VBT	4.9	4.2	3.5			
Financial difficulties	EBRT	2.0	2.3	2.0	**0.003**	0.85	0.26
	VBT	5.5	2.3	3.1			
Bowel symptoms (BS)							
Limitation daily activities due to BS	EBRT	9.0	12.7	14.1	**<0.001**	**<0.001**	**0.001**
	VBT	5.0	4.9	6.2			

Table 2. Mean scores of QLQ-C30 functioning scales and symptom ratings by treatment arm (continued)

		Questionnaire time points			p-value		
			Months		Time	Randomization	Time by randomization
		Baseline	84	120			
Faecal leakage	EBRT	4.0	12.1	13.4	**<0.001**	**<0.001**	0.06
	VBT	1.5	5.6	3.0			
Rectal blood loss	EBRT	0.4	1.2	1.0	0.08	0.06	0.51
	VBT	0.2	1.1	0.1			
Bloated feeling	EBRT	15.8	16.0	11.2	**<0.001**	0.16	0.78
	VBT	15.5	10.9	8.0			
Urinary symptoms (US)							
Frequency daytime	EBRT	33.2	35.0	43.4	**<0.001**	0.16	0.09
	VBT	36.5	32.0	33.1			
Frequency at night	EBRT	31.5	36.3	46.4	**<0.001**	0.21	0.05
	VBT	34.3	35.3	37.2			
Urinary urgency	EBRT	23.4	40.5	46.2	**<0.001**	0.20	0.05
	VBT	23.9	32.7	42.3			
Sleep deprivation due to urinary frequency	EBRT	15.3	18.9	25.8	**0.001**	0.10	0.18
	VBT	16.2	14.0	17.4			
Need to remain close to the toilet	EBRT	7.8	16.2	23.4	**<0.001**	**0.001**	**0.004**
	VBT	7.0	10.2	12.8			
Incontinence for urine	EBRT	11.5	20.4	29.8	**<0.001**	0.19	0.24
	VBT	10.6	20.8	25.5			
Dysuria	EBRT	5.3	3.9	2.2	**<0.001**	0.91	0.87
	VBT	7.9	3.2	2.0			
Limitation daily activities due to US	EBRT	3.6	12.4	14.2	**<0.001**	0.03	0.25
	VBT	3.0	7.3	7.3			
Sexual functioning and symptoms							
Sexual interest	EBRT	7.7	13.8	8.1	**<0.001**	0.24	0.26
	VBT	4.9	8.1	2.2			
Sexual activity	EBRT	5.3	7.3	5.3	**<0.001**	0.34	0.82
	VBT	2.8	6.4	0,0			
To what extent was sex enjoyable	EBRT	45.7	46.1	19.7	**0.004**	0.30	**<0.001**
	VBT	20.0	25.1	43.5			
Vaginal dryness	EBRT	30.9	29.6	25.3	0.83	0.66	0.07
	VBT	36.4	28.9	51.9			

P time: changes of quality of life scores over time. P random: difference in health-related quality of life between the two treatment groups. P time x random: quality of life score changes over time between the two treatment groups. EBRT, external-beam radiotherapy; VBT, vaginal brachytherapy;
Mean scores of earlier time points have previously been reported by Nout et al (EJC 2012).

Longitudinal analysis of 10-year HRQL follow-up for urinary symptoms showed increasing rates of urinary urgency and nocturnal frequency over time in both groups, but more so among EBRT patients (P=.05). Patients treated with EBRT reported higher rates of remaining close to the toilet because of urinary symptoms (P=.001; Table 2). Over time, increasing rates of urinary urgency were found, and at 7 years significantly more EBRT patients reported urinary urgency, a difference that was not seen in the 5-year HRQL analysis. Moderate or severe symptoms of urinary urgency were reported by 39.3% versus 25.5% (EBRT vs VBT, P=.05). Rates of sleep disturbance due to urinary frequency (13.1% vs 6.7%, P=.06) and the need to remain close to the toilet (8.4% vs 5.7%, P=.07) were slightly but nonsignificantly higher among EBRT patients (Figure 3, Table 3).
Overall, 50% of patients reported use of incontinence pads, without differences between the groups (50.6% vs 50.9%). Use of incontinence pads was reported by 85.2% of patients with urinary incontinence and 87.2% of those with limitations in daily activities due to urinary symptoms.

Table 3. Single item scores bowel, bladder and sexual symptoms at 7 years (n=196)*

	Treatment	N missing	N patients without symptoms	% of patients	N patients with mild symptoms$	% of patients	N patients with moderate/severe symptoms$	% of patients	t-test mean scores
Bowel symptoms (BS)									
Diarrhoea	EBRT	5	65	78.3%	11	13.3%	7	8.4%	**0.037**
	VBT	2	93	87.7%	12	11.3%	1	0.9%	
Limitation daily activities due to BS	EBRT	2	58	67.4%	19	22.1%	9	10.5%	**0.001**
	VBT	2	93	87.7%	11	10.4%	2	1.8%	
Faecal leakage	EBRT	3	64	75.3%	12	14.1%	9	10.6%	**0.03**
	VBT	1	91	85%	14	13.1%	2	1.8%	
Rectal blood loss	EBRT	2	84	97.7%	1	1.2%	1	1.2%	0.83
	VBT	2	103	97.2%	3	2.8%	0	0.0%	
Bloated feeling	EBRT	2	56	65.1%	21	24.4%	9	10.5%	**0.04**
	VBT	2	81	76.4%	21	19.8%	4	3.8%	
Bowel urgency	EBRT	2	38	44.2%	28	32.6%	20	23.3%	**<0.001**
	VBT	2	71	67%	28	26.4%	7	6.6%	
Flatulence	EBRT	3	36	42.4%	31	36.5%	18	21.2%	0.76
	VBT	2	54	50.9%	40	37.7%	12	11.3%	
Stomach/bowel cramps	EBRT	2	63	73.3%	18	20.9%	5	5.9%	0.12
	VBT	2	88	83.0%	14	13.2%	4	3.8%	

Table 3. Single item scores bowel, bladder and sexual symptoms at 7 years (N=196)* (continued)

	Treatment	N missing	N patients without symptoms	% of patients	N patients with mild symptoms[$]	% of patients	N patients with moderate/severe symptoms[$]	% of patients	t-test mean scores
Urinary symptoms (US)									
Frequency daytime	EBRT	5	29	34.9%	31	37.3%	23	27.7%	0.58
	VBT	2	40	37.7%	41	38.7%	25	23.6%	
Frequency at night	EBRT	3	20	23.5%	40	47.1%	25	29.4%	0.56
	VBT	2	35	33.0%	42	39.6%	29	27.4%	
Urinary urgency	EBRT	4	27	32.1%	24	28.6%	33	39.3%	**0.05**
	VBT	2	41	38.7%	38	35.8%	27	25.5%	
Sleep deprivation due to urinary frequency	EBRT	4	50	59.5%	23	27.4%	11	13.1%	0.06
	VBT	3	77	73.3%	21	20.0%	7	6.7%	
Need to remain close to the toilet	EBRT	4	54	64.3%	23	27.4%	7	8.4%	0.07
	VBT	4	82	78.8%	16	15.4%	6	5.7%	
Incontinence for urine	EBRT	4	48	57.1%	26	31.0%	10	11.9%	0.89
	VBT	4	57	54.8%	38	36.5%	9	8.7%	
Dysuria	EBRT	4	76	90.5%	5	6.0%	3	3.6%	0.35
	VBT	6	96	94.1%	4	3.9%	2	2.0%	
Limitation daily activities due to US	EBRT	1	63	72.4%	20	23.0%	4	4.6%	0.11
	VBT	1	90	84.1%	13	12.1%	4	3.7%	
Difficulties emptying of the bladder	EBRT	4	66	78.6%	13	15.5%	5	6.0%	0.19
	VBT	4	89	85.6%	12	11.5%	3	2.9%	
Sexual symptoms**									
To what extent was sex enjoyable	EBRT	65	3	13.0%	8	34.8%	12	52.2%	**0.001**
	VBT	78	15	50.0%	9	30.0%	6	20.0%	
Vaginal dryness	EBRT	67	11	52.4%	3	14.3%	7	33.4%	0.763
	VBT	78	18	60.0%	4	13.3%	8	26.7%	
Short or narrow vagina	EBRT	66	13	59.1%	8	36.4%	1	4.5%	0.190
	VBT	79	16	55.2%	7	24.1%	6	20.6%	
Pain during intercourse	EBRT	66	17	77.3%	4	18.2%	1	4.5%	0.122
	VBT	81	17	63.0%	6	22.2%	4	14.8%	

* At 7 years there were 202 responders; 6 patients were exlcuded owing to endometrial cancer recurrence or second cancer in the pelvic region.

Abbreviations: EBRT, external beam radiotherapy; VBT, vaginal brachytherapy

[$] mild symptoms: response 'a little'; moderate/severe symptoms: response "quite a bit" or "very much"

** responses to these questions were only expected if the respondent indicated to be sexually active

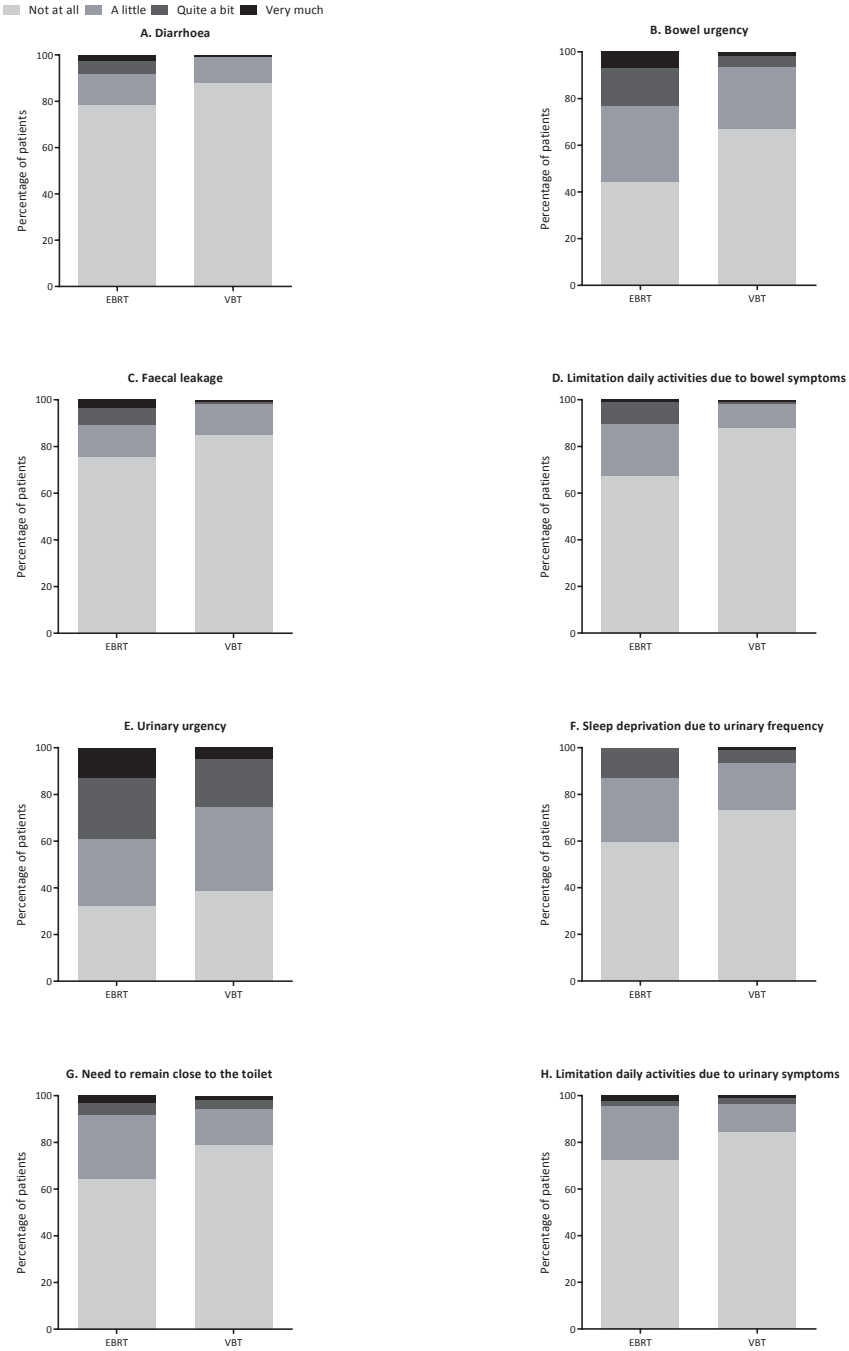

Figure 3. Patient symptom scores at 7 years for (A) diarrhea, (B) bowel urgency, (C) fecal leakage, (D) limitation of daily activities due to bowel symptoms, (E) urinary urgency, (F) sleep deprivation due to urinary frequency, (G) need to remain close to the toilet, and (H) limitation of daily activities due to urinary symptoms.

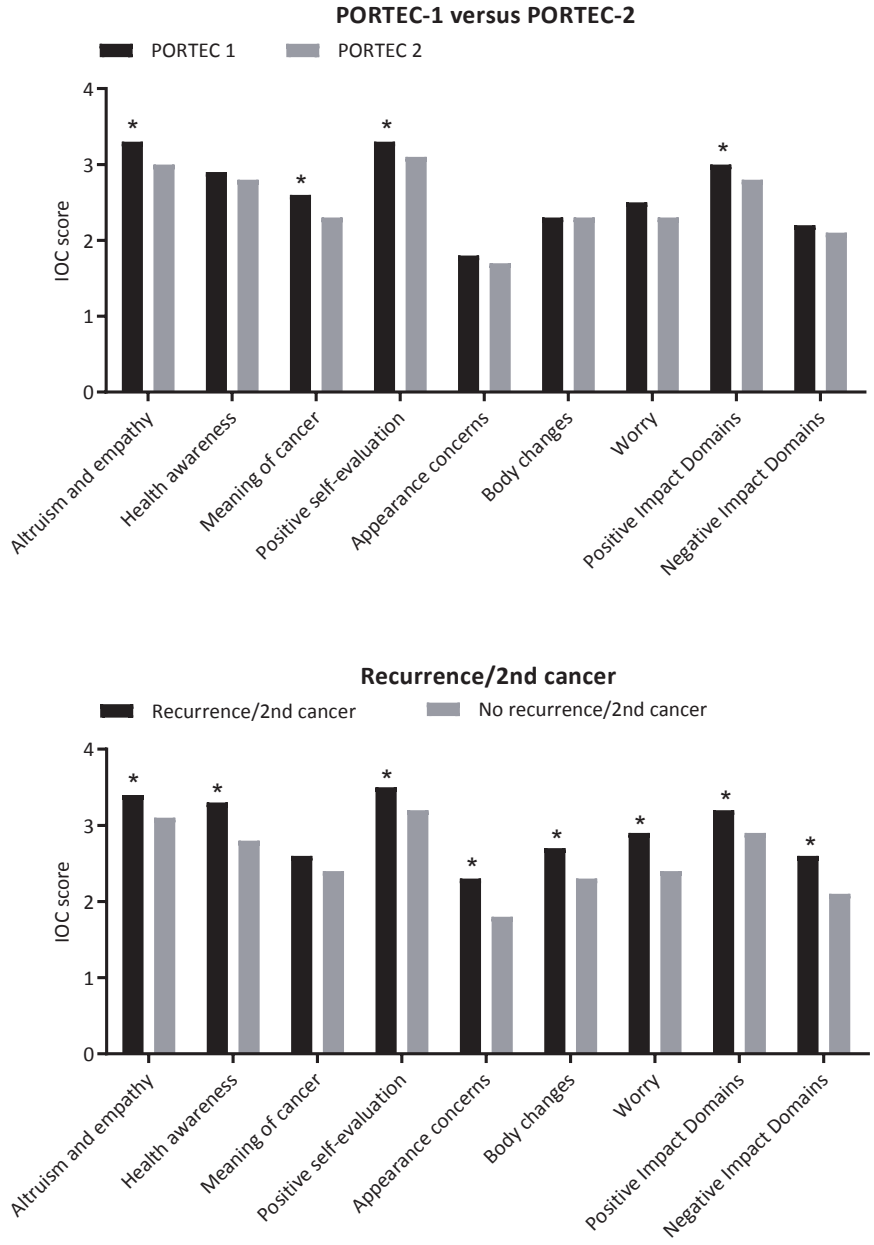

Figure 4. Impact of cancer scores at 7 years of (A) patients treated in the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 versus PORTEC-2 trial; and (B) patients in PORTEC-1 and PORTEC-2 with recurrence or a second cancer versus patients without recurrence or second cancer.

IOC scores

All scales for the IOC questionnaire could be computed for 176 of 190 patients (92.6%). No differences in any of the subscales were seen between the 2 PORTEC-2 treatment arms. Comparison of PORTEC-2 IOC scores with PORTEC-1 scores showed that PORTEC-1 patients tended to have higher scores on every subscale and overall scales (Figure 4 and Table S1. Analysis of covariance (adjusted for the presence of bone problems, having a partner, and age) showed that PORTEC- 1 patients scored higher on the positive impact domain (3.03 vs 2.82, P=.002).

Differences in IOC scores were found between the 51 patients who had reported to have been diagnosed and treated for EC recurrence or second cancer (PORTEC-1 n=39, PORTEC-2 n=12), compared with the combined general PORTEC-1 and -2 patients. These patients had significantly higher scores on all IOC subscales, except for meaning of cancer (Figure 4).

DISCUSSION

This long-term analysis of HRQL in the PORTEC-2 trial shows that EBRT may have a long-lasting, clinically relevant, mostly bowel symptom-related negative impact on HRQL, with moderate or severe limitation of daily activities reported by 10% of the patients. Patients treated with EBRT reported significantly more diarrhea, fecal leakage, urgency, and limitations in daily activities due to bowel symptoms compared with VBT. At 7 years, for the first time significantly more urinary urgency was reported by patients treated with EBRT.

This is one of the few long-term analyses of patient reported gastrointestinal and bladder symptoms after pelvic EBRT in a randomised trial, with the strengths of exclusion of biases due to the randomised comparison and the complete follow-up. Our results are consistent with the rates of gastrointestinal and bladder toxicity found in other studies.[22-24] Although the differences in mean scores were small, 10% of patients reported to have moderate or severe limitations of daily activities, and this is clinically relevant.[19, 20]

These patient-reported outcomes provide a complete picture of survivorship issues after treatment of EC, because agreement between patient- and physician-based scoring of toxicities is low, with significant underreporting of lower-grade toxicities that do impact daily life.[25] Similar to the long-term quality-of-life analysis of the PORTEC-1 trial, we found that urinary symptoms with use of incontinence pads was not reported until more than 5 years after treatment, showing the combined effects of aging and EBRT on the bladder and pelvic floor. It is known from previous studies that the bladder is a late-responding organ[8-10] and that pelvic floor dysfunction gradually develops over time.

General functioning and global health did not significantly differ between EBRT and VBT patients, suggesting that diagnosis and treatment of EC have a transient impact on patient functioning and that many patients adjust their lives to bothersome but manageable symptoms.

Sexual activity and interest were reported by only 19.4% and 28.1% of the patients at 7 years, without differences between EBRT and VBT. Patients treated with EBRT more often (87% vs 51%) reported sex to be enjoyable, whereas there were no differences in symptoms such as vaginal dryness or pain. The low activity rates together with the low completion rate of the sexual functioning questions are a limitation to these findings.

The challenge is to develop preventive and intervention measures that might reduce or prevent such long-lasting symptoms caused by EBRT. Andreyev et al[26] reported clinical improvement in bowel function with a structured, algorithm-driven approach. Pelvic floor muscle training programs for gynecologic cancer survivors with pelvic floor dysfunction showed improved results compared with no intervention[27, 28]. It remains to be seen whether instruction on simple pelvic floor exercises for all patients will reduce symptoms and dysfunction over time.

Another possible limitation to this analysis is the inherent selection of responders at long-term analysis, because participants had to be alive and disease-free. Previous analyses had shown no differences in patient or tumour characteristics between responders and non-responders.[7] The patients in the present analysis were slightly younger and had fewer comorbidities. With a mean age of the PORTEC-2 patients of 69 years, the older patients with more comorbidities were at higher risk to die of intercurrent disease compared with the younger patients. Another explanation could be that the older patients were not able to respond owing to other reasons, such as vision problems or cognitive disorders. With the high response rate of 77% at 7 years, however, these results are generally applicable.

No differences in IOC scores were seen between patients in the PORTEC-2 treatment arms. Comparison of PORTEC-1 and PORTEC-2 patients showed higher scores on positive impact scales among PORTEC-1 patients. Younger patients and those with a partner had higher scores on the positive impact domain scales, whereas patients with bone or joint problems scored higher on the negative impact scales. Oerlemans et al[12] reported in a study among non-Hodgkin lymphoma survivors fewer positive and more negative impacts of cancer in Dutch survivors compared with American non-Hodgkin lymphoma survivors. They suggested that IOC scores might be more dependent on cultural background than type of cancer. Age, length of follow-up, female gender, education level, relationship, and employment were factors of influence.[12] In Table S1 an overview of the IOC scores from these 4 different study groups is shown.

The higher IOC scores among patients who had been diagnosed with EC recurrence or second cancer reflect their having to cope with the stresses and anxieties of having had cancer for the second time, and additional symptoms of renewed treatment.

In conclusion, this study shows the long-lasting, clinically relevant, mostly bowel symptom-related negative impact of EBRT on HRQL of a significant minority of the patients, although not significantly influencing general health and overall quality of life. External beam radiation therapy should be used only when the benefit outweighs the risks of toxicity. These results provide important information to be used for patient counselling and shared decision making regarding costs and benefits of adjuvant treatment. Future studies should be aimed at methods to prevent or improve these symptoms. The reduction of such long-term symptoms might be achieved by using new radiation techniques. First studies of intensity modulated radiation therapy have shown lower rates of both acute and late symptoms.[29-31] Preventive measures for pelvic floor function should be investigated.

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SUPPLEMENTARY MATERIAL

Table S1. IOC scores of the PORTEC studies compared with Dutch and American NHL survivors

	PORTEC-1	PORTEC-2	Dutch NHL cohort	American NHL cohort
	N = 246	N = 202	N = 491	N = 738
Median age at time of questionnaire	75	75	63	63
Mean follow up duration (years)	13.4	7.1	5.3	10.2
IOC psychological: Altruism and Empathy	3.3	3.0	3.3	3.9
IOC physical: health awareness	2.9	2.8	3.2	3.7
IOC psychological: meaning of cancer	2.6	2.3	2.7	2.7
IOC psychological: positive self-evaluation	3.3	3.1	3.4	3.9
IOC physical: Appearance concerns	1.8	1.7	1.8	1.7
IOC physical: body changes	2.3	2.3	2.6	2.4
IOC worry	2.5	2.3	2.8	2.6
IOC Positive Impact Domains	3.0	2.8	3.1	3.5
IOC Negative Impact Domains	2.2	2.1	2.4	2.2

IOC, impact of cancer; NHL, non-hodgkin lymphoma; Dutch NHL cohort; Eindhoven registration study, American NHL cohort; North-Carolina registration study

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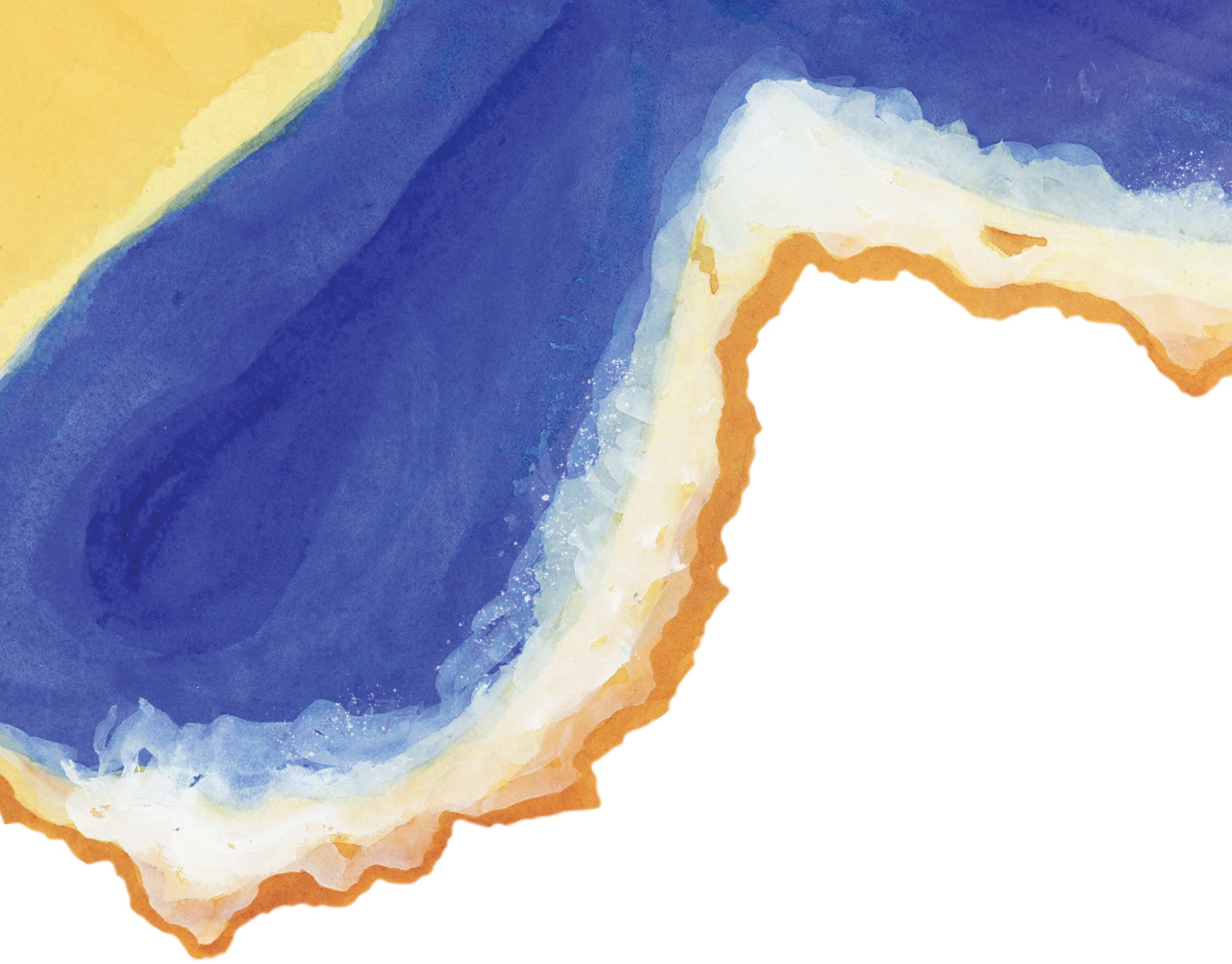

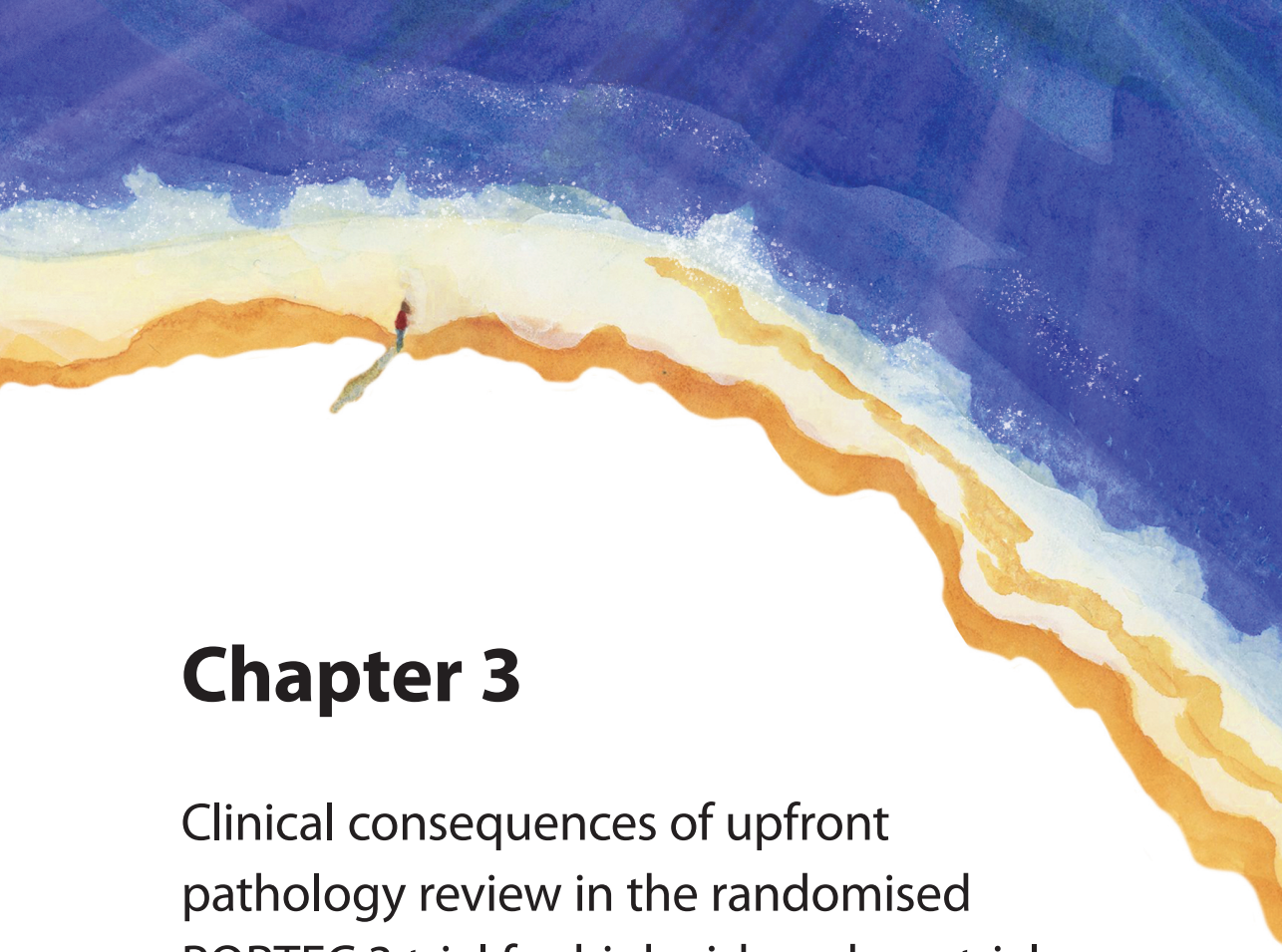

Chapter 3

Clinical consequences of upfront pathology review in the randomised PORTEC-3 trial for high-risk endometrial cancer

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ABSTRACT

Background

In the PORTEC-3 trial, women with high-risk endometrial cancer (HREC) were randomised to receive pelvic radiotherapy (RT) with or without concurrent and adjuvant chemotherapy (two cycles of cisplatin 50 mg/m^2 in weeks 1 and 4 of RT, followed by four cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2). Pathology review was required before patient enrolment. The aim of this analysis was to evaluate the role of central pathology review before randomisation.

Patients and methods

A total of 1295 cases underwent pathology review to confirm HREC in the Netherlands (n= 395) and the UK (n= 900), and for 1226/1295 (95%) matching review and original reports were available. In total, 329 of these patients were enrolled in the PORTEC-3 trial: 145 in the Netherlands and 184 in the UK, comprising 48% of the total PORTEC-3 cohort of 686 participants. Areas of discrepancies were evaluated, and inter-observer agreement between original and review opinion was evaluated by calculating the kappa value (κ).

Results

In the 1226 pathology reviews, 6356 selected items were evaluable for both original and review pathology. In 43% of cases at least one pathology item changed after review. For 102 patients (8%), this discrepancy led to ineligibility for the PORTEC-3 trial, most frequently due to differences in the assessment of histological type (34%), endocervical stromal involvement (27%) and histological grade (19%). Lowest inter-observer agreement was found for histological type (κ=0.72), lymph-vascular space invasion (κ=0.72) and histological grade (κ=0.70).

Conclusion

Central pathology review by expert gynaeco-pathologists changed histological type, grade or other items in 43% of women with HREC, leading to ineligibility for the PORTEC-3 trial in 8%. Upfront pathology review is essential to ensure enrolment of the target trial-population, and to avoid over- or undertreatment, especially when treatment modalities with substantial toxicity are involved.

This study is registered with ISRCTN (ISRCTN14387080, www.controlled-trials.com) and with ClinicalTrials.gov (NCT00411138).

INTRODUCTION

Adjuvant treatment of women with endometrial cancer (EC) is based on clinicopathological risk factors, such as histological grade, myometrial invasion, age and lymph-vascular space invasion (LVSI).[1–3] A minority of patients (15%) have high-risk disease features, which include endometrioid endometrial carcinoma (EEC) of FIGO stage I grade 3 with deep invasion or with substantial LVSI; stage II or III EEC; or non-endometrioid histologies (NEEC) stage I–III.[1–4] For these patients higher risks of distant metastases and EC-related death have been reported, and adjuvant chemotherapy may be considered.[5–8]

As these high-risk criteria comprise different features of the pathology diagnosis, reproducibility is essential. Studies of pathology review by expert subspecialty pathologists, however, have shown that evaluation of female reproductive tract pathology had the highest rates of discrepancies between original and review pathology assessment including discrepancies with consequences for treatment.[9] Challenges for pre-treatment pathology review are that review is time-consuming and expensive, that timelines are tight and logistical procedures are complicated.

The PORTEC-3 trial is an international randomised phase III trial of adjuvant therapy in high-risk EC (HREC). Women with HREC were randomly allocated (1 : 1) to pelvic radiotherapy (RT) alone or RT plus concurrent and adjuvant chemotherapy. Primary end points are overall survival and failure-free survival. To select patients with true HREC and avoid unnecessary intensive treatment in lower-risk cases, upfront pathology review was carried out by expert gynaeco-pathologists of the participating groups to confirm HREC and eligibility for the study.

The current analysis was done to establish the value of upfront pathology review. The aims were to explore the proportion of patients who were ineligible for the PORTEC-3 trial after pathology review, and to evaluate inter-observer variability between original and review pathology assessments.

METHODS

Study design and participants

PORTEC-3 is a randomised Intergroup trial led by the Dutch Gynaecological Oncology Group, with participating groups MRC-NCRI (UK), ANZGOG (Australia and New Zealand), MaNGO (Italy), Fedegyn (France) and CCTG (Canada). Surgery comprised hysterectomy with salpingo-oophorectomy. Lymphadenectomy was at the discretion of the participating centres. For serous or clear cell cancers, surgical staging including omentectomy; peritoneal biopsies and lymphadenectomy was recommended.

Details on patient selection and treatment have been described in a previous publication.[10] Eligible patients had EEC of FIGO 2009 stage 1A grade 3 with LVSI; IB grade 3; stage II, IIIA, $IIIB_{parametrial}$ or IIIC; or NEEC stage IA–III. Patients were randomised (1 : 1) to RT (48.6 Gy) or RT plus adjuvant chemotherapy (two cycles of cisplatin 50 mg/m^2 in weeks 1 and 4 of RT, followed by four cycles of carboplatin AUC5 and paclitaxel 175mg/m^2 every 3 weeks).

Written informed consent (IC) was obtained from all patients. The protocol was approved by the Dutch Cancer Society and the Ethics committees. Participating groups obtained their own IRB and ethics approvals and were funded by separate grants.

Procedures

Each participating group had appointed expert gynaeco-pathologists as reviewers for the study. After surgery, the pathology diagnosis was made by the regional pathologist. In case of HREC, all histopathology slides and a copy of the pathology report were sent for pathology review as part of patient management, to confirm HREC within 1 week, with the aim to ensure that only true HREC cases were informed and enrolled in the trial. If IC was given, pathology review for the PORTEC-3 trial was completed with trial-specific items. Upon consent for storage of tumour tissue for translational research a formalin-fixed paraffin-embedded (FFPE)-block was centrally stored. All other blocks and slides were sent back to the referring centre.

The items for original and review pathology included WHO histological type, grade, depth of myometrial invasion, distance to serosa or serosal breach, LVSI, cervical stromal involvement, involvement of the tubes and/or ovaries and lymph node involvement. Histological type was evaluated as endometrioid, serous, clear cell, mixed (endometrioid with serous/clear cell components), mucinous, or other histologies according to WHO-classification.[11] Mixed tumours were classified as serous or clear cell when this component was at least 25%, otherwise as mixed. Mucinous tumours were grouped with EEC for analysis. Histological grading was done according to WHO.[11] NEEC was considered high grade per definition (grade 3). The differences in histological grading between original and review pathology were evaluated for EEC. Immunohistochemistry (IHC) was carried out only incidentally, at the discretion of the review pathologist and only if FFPE-blocks were available at time of the central review process.

For the current analysis, anonymised original and review pathology reports from both randomised and non-randomised patients in the Netherlands (NL) and the UK (UK) were assessed. These two countries were chosen as they had the largest number of patients in the trial (together 48%) and all pathology reviews had been done at two centres in each country. For the UK patients, the review pathologist provided a short confirmation of HREC and eligibility. For the randomised patients, the review report was completed after IC was given.

Outcomes

Discrepancies between original and central pathology review were assessed as discrepancies with and without change of eligibility for the PORTEC-3 trial. Reasons for non-eligibility were checked by two expert gynaeco-pathologists (TB and NS).

Statistical analysis

The data were collected in a SPSS database (version 23.0). For the comparison of the pathology items, Cohen's kappa value (κ) was used.[12] For the interpretation of the κ values the scale proposed by Landis and Koch was used.[13]

Differences between eligible women who were included or declined the study were analysed by the χ^2 test. Items with P-values <0.05 were considered significant.

RESULTS

Population and compliance

The PORTEC-3 trial included 686 patients (2006–2013), of whom 145 were recruited in NL and 184 in the UK. Slides from 1295 patients (395 NL, 900 UK) were sent for pathology review. Fifteen original pathology reports (9 NL, 6 UK) were not available for analysis. Fifty-four patients (18 NL, 36 UK) were ineligible based on the original pathology report, which was confirmed by pathology review and they were therefore excluded from the analysis. A total of 1226 patients (368 NL, 858 UK) were eligible based on local pathology and were included in this analysis (see Figure 1, Table 1 and supplementary Table S1).

Discrepancies and inter-observer variability

A total of 6356 pathology items were evaluable for both original and review pathology. For 679 items (11%) there was a discrepancy between original and review pathology. The highest agreement was found for serosal breach (98%) and cervical stromal involvement (94%), and most disagreement for histological type (15%) and grade (20%; see Table 2). In 532 cases (43%) at least one pathology item changed after review, which led to ineligibility for the PORTEC-3 trial in 8% (n= 102; Table 3). Most frequent reasons were change of histological type (34%, n=35), cervical stromal involvement (27%, n= 27) and change of histological grade in 19% (n=19), which was similar between the NL and UK cohorts. Eighty-three of these 102 became low risk after central pathology review, while in 19 cases the histological type was reclassified as carcinosarcoma; these were therefore still high risk but were not eligible for the PORTEC-3 trial.

Highest rates of inter-observer variability were found for histological type (κ=0.72), LVSI (κ =0.72) and histological grade (κ=0.70; Table 2). See supplementary Table S2, for results by country and supplementary Figure S3. Lowest inter-observer variability was

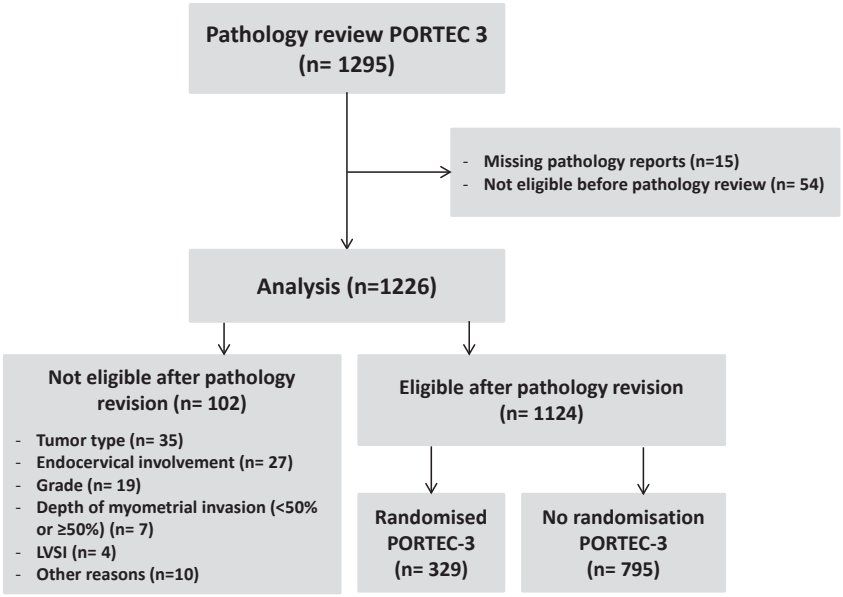

Figure 1. CONSORT diagram

Table 1. Major pathology criteria of the eligible patients (n=1226)

Major pathologic criteria		**NL patients (N=368)**		**UK patients (N=858)**	
		n	**%**	***n***	**%**
Age	< 60	100	37%	239	28%
	60-69	110	41%	373	44%
	≥ 70	58	22%	243	28%
	Missing	100		3	
FIGO stage (2009)	IA	72	20%	138	16%
	IB	93	26%	178	21%
	II	99	27%	263	31%
	IIIA	43	12%	97	12%
	IIIB	18	5%	62	7%
	IIIC	40	11%	101	12%
	Missing	3		19	
Histological type	Endometrioid or mucinous	262	71%	501	59%
	Serous or mixed serous	66	18%	193	23%
	Clear cell or mixed clear cell	31	8%	111	13%
	Other*	9	2%	45	5%
	Missing	0		8	

Table 1. Major pathology criteria of the eligible patients (n=1226) (continued)

Major pathologic criteria		NL patients (N=368)		UK patients (N=858)	
		n	%	*n*	%
Histological grade	1	81	22%	155	18%
	2	53	14%	135	16%
	3	127	35%	201	24%
	NEEC	107	29%	354	42%
	Missing	0		13	
Myometrial invasion	< 50 %	135	37%	215	38%
	≥ 50 %	233	63%	346	62%
	Missing	0		297	
Growth through serosa	Yes	21	6%	31	4%
	No	346	94%	675	96%
	Missing	1		152	
Cervical glandular involvement	Yes	135	38%	172	43%
	No	224	62%	230	57%
	Missing	9		456	
Cervical stromal involvement	Yes	138	38%	339	47%
	No	225	62%	382	53%
	Missing	5		137	
LVSI	Yes	198	54%	287	60%
	No	169	46%	194	40%
	Missing	1		377	
Involvement of the ovaries	Yes	46	13%	67	9%
	No	322	87%	666	91%
	Missing	0		125	
Lymph node involvement	Not applicable	252	69%	553	66%
	No malignancy	73	20%	184	22%
	Metastasis	41	11%	101	12%
	Missing	2		20	
Parametrial involvement	Yes	24	13%	61	16%
	No	167	87%	326	84%
	Missing	177		471	

Missing values were not taken into account to the percentages.

The pathology criteria of the NL versus the UK patients were based on review pathology

* other histology includes undifferentiated, carcinosarcoma or mixed combinations other than serous/clear cell with endometrioid.

FIGO: International Federation of Gynecology and Obstetrics; LVSI: lymph-vascular space invasion; EEC: endometrioid endometrial cancer; NEEC: non-endometrioid endometrial cancer

found for cervical stromal invasion (κ=0.87), with overall agreement of 94%. However, a discrepancy here led to ineligibility for the trial in 27/69 (39%) of cases.
Serosal breach was present in only 5% of cases. Although agreement was high for both countries (97% and 99%), κ values differed (NL κ=0.83 versus UK κ=0.63), showing that κ values are less reliable for items with few observations.

Histological type and grade

Figure 2 shows the agreement of histological classification and grade. Overall agreement of histological type was 85%; discrepancies led to ineligibility in 19% of cases (Table 2). Discrepancies were found for all histologies, although the agreement was highest for EEC.
The overall agreement for histological grade was 80%; 16% (n=113) were downgraded at review pathology, with most frequent shifts (76 cases) from grade 2 to 1. In 4% (n= 26), the grade was higher at review.

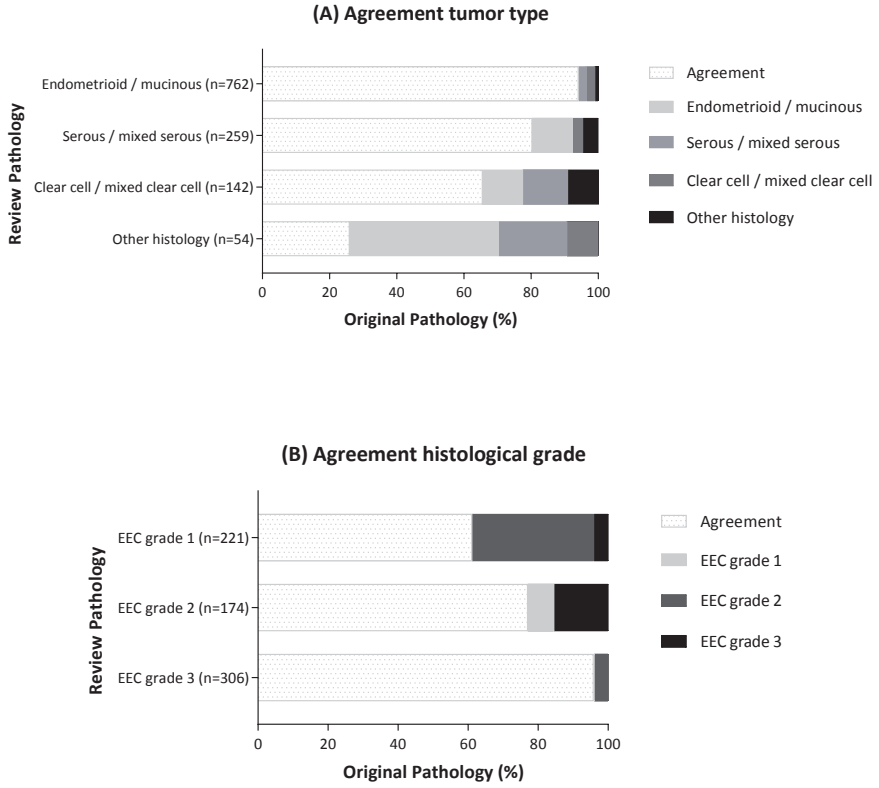

Figure 2. Histological type (A) and histological grade evaluation (B) in original and review pathology.

Table 2. Inter-observer variability between original and review pathology report for the total cohort.

Total cohort									
Pathology variables	**Total number available for analysis***	**Missing items**	**Total discrepancies**	**Disagreement % #**	**Leading to ineligibility**	**Leading to ineligibility % $**	**Not leading to ineligibility**	**Not leading to ineligibility % ¥**	**κ value**
Histological type	1217	9	185	15%	35	19%	150	81%	0.72
Histological grade (EEC only)	701	0	139	20%	19	14%	120	86%	0.70
Myometrial invasion	923	304	88	10%	7	8%	81	92%	0.79
Cervical glandular involvement	626	600	73	12%	0	0%	73	100%	0.73
Cervical stromal involvement	1063	163	69	6%	27	39%	42	61%	0.87
LVSI	762	464	101	13%	4	4%	97	96%	0.72
Growth through serosa	1064	162	24	2%	0	0%	24	100%	0.76
Total	6356	1702	679	11%	92	14%	587	86%	NA

* Total number of pathology items available for comparison between original and review pathology.
# Total discrepancies / total number of pathology items available for analysis.
$ number of pathology items leading to inelegibility / total discrepancies.
¥ number of pathology items not leading to ineligibility / total discrepancies.
LVSI; lymph vascular space invasion. EEC; endometrioid endometrial cancer

Table 3. Reasons for ineligibility of 102 patients based on pathological review report

Pathology variables	**cohort (*n*=102)**		**NL cohort (*n*=42)**		**UK cohort (*n*=60)**	
	n	**%**	***n***	**%**	***n***	**%**
Histological type	35	34%	14	33%	21	35%
Histologic grade[#]	19	19%	7	17%	12	20%
Myometrial invasion	7	7%	3	7%	4	7%
Cervical involvement	27	27%	12	29%	15	25%
LVSI	4	4%	2	5%	2	3%
Other[±]	10	10%	4	10%	6	10%
Total ineligible patients	102	100%	42	100%	60	100%
Percentage of total cohort	102	8%	42	11%	60	7%

[#] grade shift for endometrioid endometrial carcinoma.
[±] Other reasons included absence of involvement of the ovaries, tube or parametrium, or other primary tumour site (cervix, tube or adnex).
LVSI; lymph vascular space invasion. NL; Netherlands. UK; United Kingdom.

DISCUSSION

In the PORTEC-3 trial of adjuvant RT with or without chemotherapy for women with HREC, upfront pathology review was carried out before patient counselling to ensure that only true HREC patients were informed about the trial, and that the trial only enrolled true HREC cases. The expert gynaeco-pathology review changed the eligibility for 102 women (8%), most frequently due to changes in histological type or cervical stromal involvement. These lower-risk patients did therefore not risk receiving more intensive and potentially toxic treatment. Furthermore, a true HREC study population in the PORTEC-3 trial was ensured. For 19 patients the histological type changed to carcinosarcoma and although they were high risk, they were not eligible for the trial.

The inter-observer agreement between original and review pathology was highest for cervical stromal invasion. The most frequent discrepancies were found for histological type, histological grade and presence of LVSI. While many of these discrepancies did not affect eligibility for the current study, they were important for prognosis and adjuvant treatment of patients in clinical practice.

Discrepancies in gynaeco-pathology diagnosis between original and review pathology have been reported before. A Canadian study reported EC as the tumour site with most frequent differences in pathological assessment.[14] Another Canadian cohort reported major discrepancies in 8% of biopsies and hysterectomy specimens taken together, and in 12% of hysterectomy specimens. The most frequent diagnostic discrepancies were assessment of myometrial invasion and histological subtype.[15]

In the PORTEC-1 and -2 trials pathology review showed that 24% and14%, respectively, of patients were in retrospect ineligible, while this was 8% for the PORTEC-3 trial.[1, 16, 17] Eligibility in the PORTEC-1 and -2 studies was determined by grade, myometrial invasion and histological type. Differences in eligibility were often caused by shift of grade 2 to grade 1, while such grade shift did not affect the PORTEC-3 trial where patients had to have either grade 3 or NEEC or advanced stages. Minor discrepancies in grade or histology changed the eligibility for the PORTEC-3 trial in only a minority of patients. However, some shift of grade 2 to grade 1 was seen in the PORTEC-3 trial as well. Previous studies have shown that the intermediate grade is the least reproducible and that a two-tiered grading system assessing high versus low grade would be preferable.[18–20] The lower inter-observer variation in the current study could also reflect the increasing standardisation of pathology criteria and subspecialty training.

Frequent causes of discrepancies were assessment of histological type and cervical involvement. Several studies have addressed challenges in diagnosing serous, clear cell and mixed cancers, the level of agreement varying from 62% to 83%.[21–23] In the study by Han et al,[21] there was consensus on histological type in 72% of cases. With a panel

of three IHC markers the agreement increased to 96%.[21] The use of IHC was not routine practice in the period of the PORTEC-3 trial and was only carried out in incidental cases. Variations in defining cervical stromal involvement have also been reported in a study of 76 cases reviewed by 6 expert gynaecopathologists with agreement in only 50%. Difficulties comprised the definition of the junction between the lower uterine segment and the endocervix, and the distinction between unattached tumour components or true cervical stromal involvement.[24]

A limitation of this study could be that the pathology reviews took place at four university centres, and inter-observer variations between these gynaeco-pathologists were not assessed. The percentages of major discrepancies were, however, quite similar between the two countries. In the PORTEC-2 trial, higher risk of distant metastasis and lower survival were found for patients who were considered 'high-risk' after central review pathology, suggesting that the review pathology was more reliable to predict prognosis when compared with the original pathology.[16]

Creating a well-defined trial population with confirmed eligibility by upfront pathology review should be considered the standard for future scientific studies. Expert consultation is being increasingly used, but pathology review might not be part of the standard procedure, because it is time consuming and expensive. To this purpose, further standardisation of pathology criteria, expert education and subspecialisation in gynaeco-pathology are essential, as well as rapid access to expert consultation. The transition to digital pathology will greatly facilitate rapid consultation. Introduction of IHC and molecular analysis using the TCGA molecular subgroup classification will further improve risk assignment.[25, 26]

A substantial proportion of eligible women declined participation in the trial, mostly because they did not want to receive chemotherapy. Younger patients and those with a more advanced stage of disease more often consented to participate in the trial (supplementary Table S1). The potential treatment consequences for patients should be the main reason to incorporate pathology review in daily practice. In the current study, most patients with discrepancies were downgraded and were spared unnecessary treatment.

In conclusion, upfront pathology review by expert gynaecopathologists identified changes in histological type, grade or other items in 43% of patients. Of these, 8% of patients were found ineligible for the trial. This resulted in a true HREC population and reliable pathology assessment in the PORTEC-3 trial, which ensures the quality of future translational research. Upfront pathology review is to be preferred in future gynaecological oncology trials and in daily practice. The transition to digital pathology will strongly facilitate rapid expert pathology consultation.

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SUPPLEMENTARY MATERIAL

Table S1. Major pathology criteria of the eligible patients (n=1226). The pathology criteria of the randomised versus the non-randomised patients were based on review pathology.

Major pathologic criteria		**Randomised eligible patients (N=329)**		**Non-randomised eligible patients (N=897)**		
		N	**%**	**N**	**%**	**p-Value**
Age	< 60	141	43%	198	25%	
	60-69	136	41%	347	44%	
	≥ 70	52	16%	249	31%	
	Missing	0		103		**<0.001**
FIGO stage (2009)	IA	43	13%	167	19%	
	IB	61	19%	210	24%	
	II	97	30%	265	30%	
	IIIA	48	15%	92	11%	
	IIIB	28	9%	52	6%	
	IIIC	51	16%	90	10%	
	Missing	1		21		**0.002**
Histological type	Endometrioid or mucinous	207	63%	556	63%	
	Serous or mixed serous	70	21%	189	21%	
	Clearcell or mixed clear cell	43	13%	99	11%	
	Other*	9	3%	45	5%	
	Missing	0		8		0.295
Histological grade	EEC grade 1	63	19%	173	20%	
	EEC grade 2	47	14%	141	16%	
	EEC grade 3	95	29%	233	26%	
	NEEC	124	38%	337	38%	
	Missing	0		13		0.795
Myometrial invasion	< 50%	112	35%	238	39%	
	≥ 50 %	206	65%	373	61%	
	Missing	11		286		0.414
Growth through serosa	Yes	17	5%	35	5%	
	No	299	95%	722	95%	
	Missing	13		140		0.599
Cervical glandular involvement	Yes	142	46%	165	37%	
	No	170	54%	284	63%	
	Missing	17		448		0.015
Cervical stromal involvement	Yes	154	48%	323	42%	
	No	166	52%	441	58%	
	Missing	9		133		0.077

Table S1. Major pathology criteria of the eligible patients (n=1226). The pathology criteria of the randomised versus the non-randomised patients were based on review pathology. (continued)

Major pathologic criteria		Randomised eligible patients (N=329)		Non-randomised eligible patients (N=897)		
		N	%	N	%	p-Value
LVSI	Yes	186	58%	299	57%	
	No	135	42%	228	43%	
	Missing	8		370		0.695
Involvement of the ovaries	Yes	58	18%	55	7%	
	No	265	82%	723	93%	
	Missing	6		119		**<0.001**
Lymph node involvement	Not applicable	205	63%	600	68%	
	No malignancy	69	21%	188	21%	
	Metastasis	52	16%	90	10%	
	Missing	3		19		0.022
Parametrial involvement	Yes	32	13%	53	16%	
	No	217	87%	276	84%	
	Missing	80		568		0.273

Missing values were not taken into account to the percentages or the p-values. * other histology includes undifferentiated, other mixed combinations

FIGO: International Federation of Gynecology and Obstetrics; LVSI: lymph-vascular space invasion; EEC: endometrioid endometrial cancer; NEEC: non-endometrioid endometrial cancer

Table S2. Inter-observer variability between original and review pathology report for the NL and UK cohorts seperately.

Pathology item	Total number available for analysis*	Missing items	Total discrepancies	Disagreement %#	Leading to ineligibility	Leading to ineligibility %$	Not leading to ineligibility	Not leading to ineligibility %¥	Kappa value
NL cohort									
Histological type	368	0	58	16%	14	24%	44	76%	0.65
Histological grade (EEC only)	236	0	51	22%	7	14%	44	86%	0.65
Myometrial invasion	366	2	33	9%	3	9%	30	91%	0.80
Cervical glandular involvement	311	57	41	13%	0	0%	41	100%	0.66
Cervical stromal involvement	357	11	33	9%	12	36%	21	64%	0.80
LVSI	287	81	37	13%	2	5%	35	95%	0.73
Growth through serosa	360	8	12	3%	0	0%	12	100%	0.65
Total	2285	159	265	12%	38	14%	227	86%	NA
UK cohort									
Histological type	849	9	127	15%	21	17%	106	83%	0.74
Histological grade (EEC only)	465	0	88	19%	12	14%	76	86%	0.71
Myometrial invasion	557	301	55	10%	4	7%	51	93%	0.79
Cervical glandular involvement	315	543	32	10%	0	0%	32	100%	0.78
Cervical stromal involvement	706	152	36	5%	15	42%	21	58%	0.90
LVSI	475	383	65	14%	2	3%	63	97%	0.72
Growth through serosa	704	154	12	2%	0	0%	12	100%	0.82
Total	4071	1542	415	10%	54	13%	361	87%	NA

* Total number of pathology items available for comparison between original and review pathology.

Total discrepancies / total number of pathology items available for analysis.

$ number of pathology items leading to inelegibility / total discrepancies.

¥ number of pathology items not leading to ineligibility / total discrepancies.

LVSI; lymph vascular space invasion. EEC; endometrioid endometrial cancer

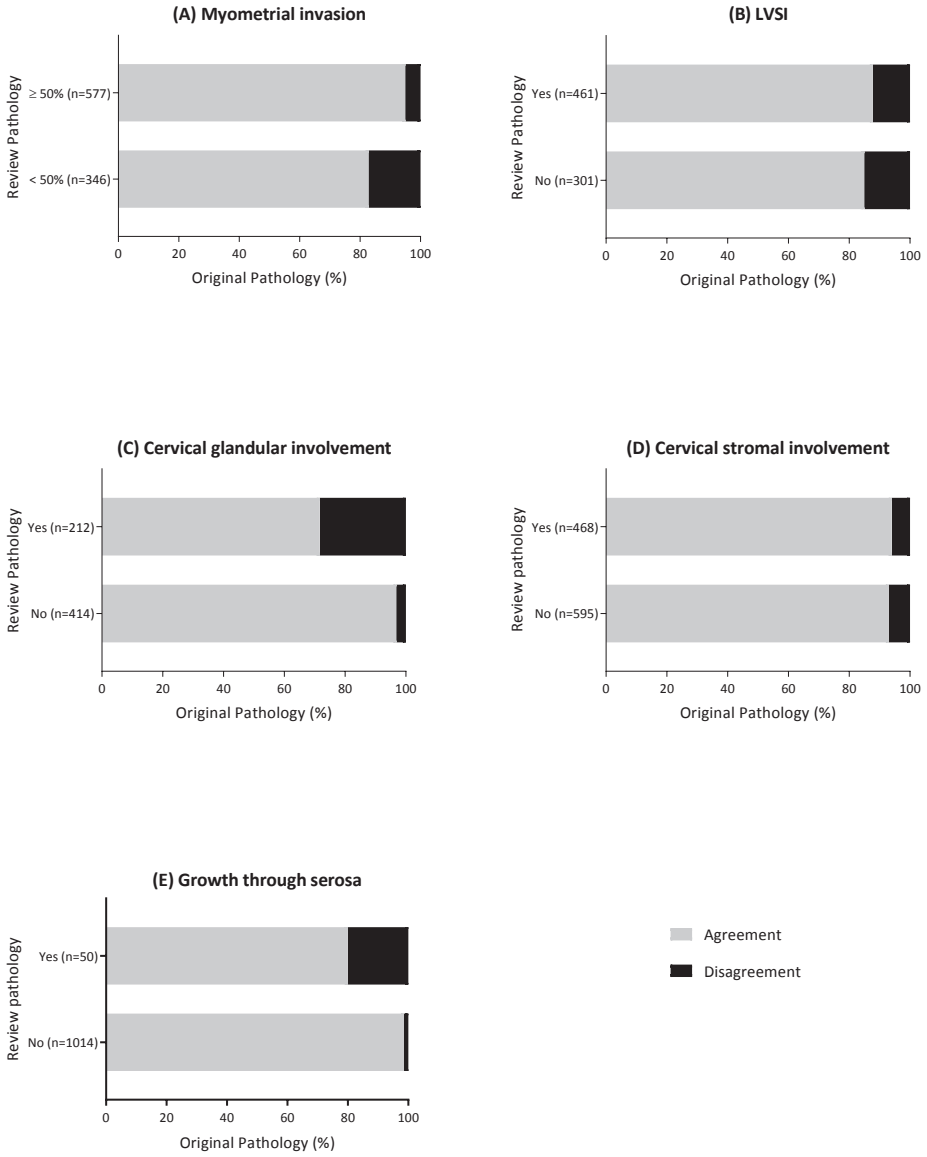
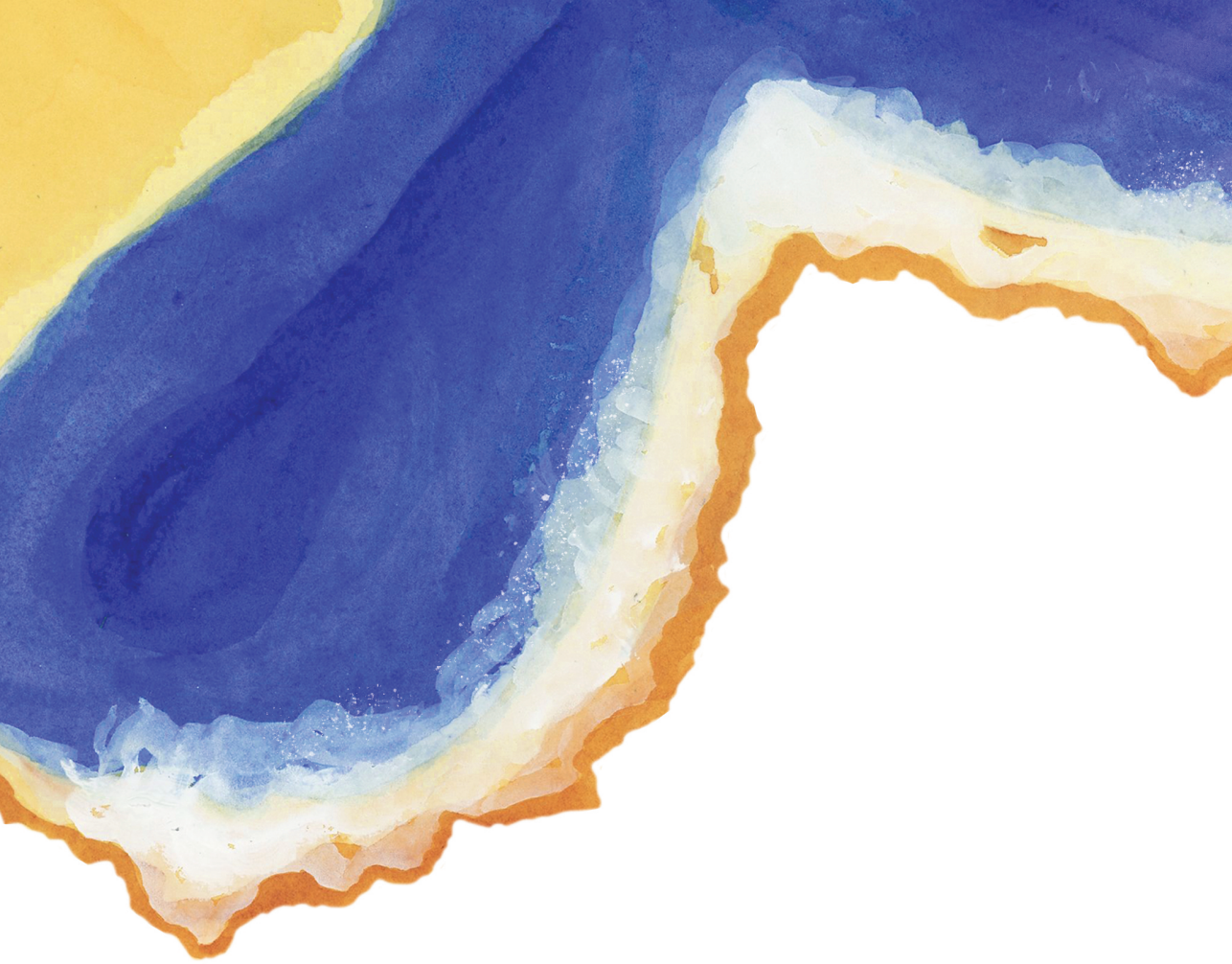
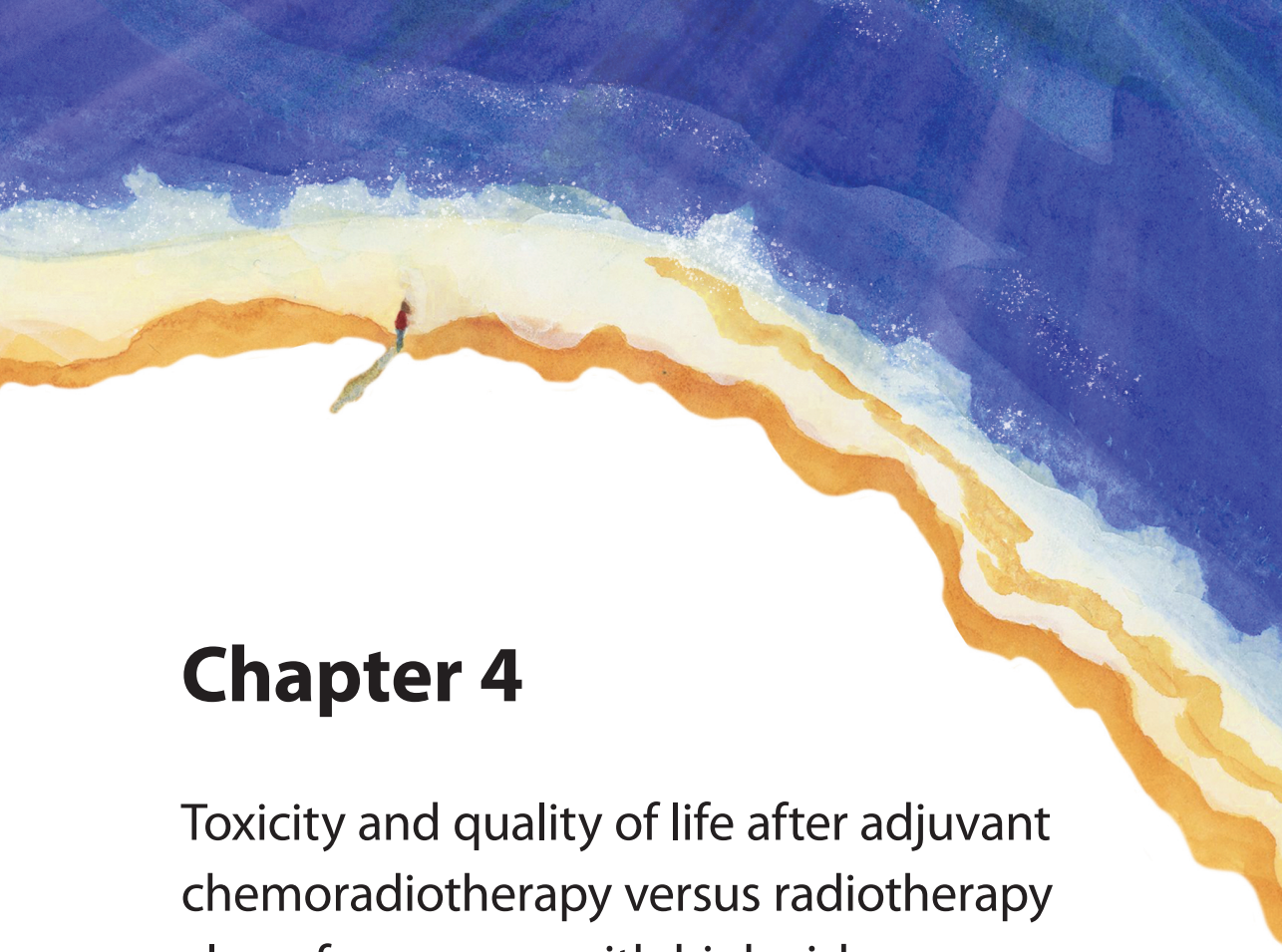


Figure S3. Review and original pathology for (A) myometrial invasion, (B) LVSI, (C) cervical glandular involvement, (D) cervical stromal involvement and (E) growth through serosa.





Chapter 4

Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial

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The Lancet Oncology 2016; 17(8): 1114-1126.

ABSTRACT

Background

About 15% of patients with endometrial cancer have high-risk features and are at increased risk of distant metastases and endometrial cancer-related death. We designed the PORTEC-3 trial to investigate the benefit of adjuvant chemoradiotherapy compared with radiotherapy alone for women with high-risk endometrial cancer.

Methods

PORTEC-3 was a multicentre, open-label, randomised, international trial. Women with high-risk endometrial cancer were randomly allocated (1:1) to radiotherapy alone (48.6 Gy) in 1.8 Gy fractions five times a week or chemoradiotherapy (two cycles concurrent cisplatin 50 mg/m^2 and four adjuvant cycles of carboplatin area under the curve [AUC] 5 and paclitaxel 175 mg/m^2) using a biased coin minimisation procedure with stratification for participating centre, lymphadenectomy, stage of cancer, and histological type. The primary endpoints of the PORTEC-3 trial were overall survival and failure-free survival analysed in the intention-to-treat population. This analysis focuses on 2-year toxicity and health-related quality of life as secondary endpoints; analysis was done according to treatment received. Health-related quality of life was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) the cervix cancer module and chemotherapy and neuropathy subscales of the ovarian cancer module at baseline, after radiotherapy and at 6, 12, 24, 36, and 60 months after randomisation. Adverse events were graded with Common Terminology Criteria for Adverse Events version 3.0. The study was closed on Dec 20, 2013, after achieving complete accrual, and follow-up remains ongoing for the primary outcomes analysis. This trial is registered with ISRCTN.com, number ISRCTN14387080, and with ClinicalTrials.gov, number NCT00411138.

Findings

Between Sept 15, 2006, and Dec 20, 2013, 686 women were randomly allocated in the PORTEC-3 trial. Of these, 660 met eligibility criteria, and 570 (86%) were evaluable for health-related quality of life. Median follow-up was 42.3 months (IQR 25.8–55.1). At completion of radiotherapy and at 6 months, EORTC QLQ-C30 functioning scales were significantly lower (worse functioning) and health-related quality of life symptom scores higher (worse symptoms) for the chemoradiotherapy group compared with radiotherapy alone, improving with time. At 12 and 24 months, global health or quality of life was similar between groups, whereas physical functioning scores remained slightly lower in patients who received chemoradiotherapy compared with patients who received radiotherapy alone. At 24 months, 48 (25%) of 194 patients in the chemoradiotherapy

group reported severe tingling or numbness compared with 11 (6%) of 170 patients in the radiotherapy alone group (p<0.0001). Grade 2 or worse adverse events were found during treatment in 309 (94%) of 327 patients in the chemoradiotherapy group versus 145 (44%) of 326 patients in the radiotherapy alone group, and grade 3 or worse events were found in 198 (61%) of 327 patients in the chemoradiotherapy group versus 42 (13%) of 326 patients in the radiotherapy alone group (p<0.0001), with most of the grade 3 adverse events being haematological (45%). At 12 and 24 months, no significant differences in grade 3 or worse adverse events were found between groups; only grade 2 or higher sensory neuropathy adverse events persisted at 24 months (25 [10%] of 240 patients in the chemoradiotherapy group *vs* one [<1%] of 247 patients in the radiotherapy alone group; p<0.0001).

Interpretation

Despite the increased physician and patient-reported toxicities, this schedule of adjuvant chemotherapy given during and after radiotherapy in patients with high-risk endometrial cancer is feasible, with rapid recovery after treatment, but with persistence of patient-reported sensory neurological symptoms in 25% of patients. We await the analysis of primary endpoints before final conclusions are made.

Funding

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INTRODUCTION

Endometrial cancer is most commonly diagnosed at an early stage and most women are cured with surgery alone.[1] Adjuvant treatment for early stage endometrial cancer is based on risk factors, such as histological grade, myometrial invasion, age, and lymph-vascular space invasion.[2–4] The PORTEC-2 trial[5,6] showed the efficacy of vaginal brachytherapy in reducing vaginal recurrence of endometrial cancer in women with high-intermediate-risk endometrial cancer. About 15% of all patients with endometrial cancer have high-risk disease (classified as stage I grade 3 cancer with deep invasion or with substantial lymph-vascular space invasion, stage II or III cancer, or cancer with non-endometrioid histology).[1] Higher incidence of distant metastases and endometrial cancer-related deaths has been reported for these patients.[7–10] Serous and clear cell endometrial cancer are histological subtypes with poorer prognosis because of their high risk of metastasis, but when diagnosed at an early stage seem to have similar survival rates to grade 3 endometrioid endometrial cancer.[11]

Pelvic external beam radiotherapy has been the standard adjuvant treatment for women with high-risk endometrial cancer for several decades. Randomised trials[12,13] comparing adjuvant chemotherapy with external beam radiotherapy have shown similar rates of relapse and survival. Because increased pelvic relapse has been reported with adjuvant chemotherapy alone, use of pelvic radiotherapy combined with adjuvant chemotherapy has been advocated.[14,15] The RTOG9708 phase 2 trial[16] investigated a combination of external beam radiotherapy with two cycles of cisplatin, followed by four cycles of cisplatin-paclitaxel in 46 women with high-risk endometrial cancer. 4-year overall survival was 85% and disease-free survival was 81%, and acceptable toxicity was reported. The randomised NSGO-EC-9501/EORTC-55991 trial compared external beam radiotherapy alone with external beam radiotherapy and four cycles of platinum-based chemotherapy. This trial was published in a pooled analysis with the MaNGO ILIADE-III trial[17] with a combined total of 534 patients, and showed statistically significantly improved progression-free survival with the addition of chemotherapy. None of these trials have reported detailed toxicity or quality of life data for chemoradiotherapy in endometrial cancer. Establishing both the benefit of more intensive adjuvant treatment and the effect in terms of added morbidity and effect on health-related quality of life are essential.

We initiated the international PORTEC-3 trial to investigate survival benefit and toxicities of chemotherapy combined with external beam radiotherapy compared with external beam radiotherapy alone for high-risk endometrial cancer. Final analysis of overall survival and failure-free survival is awaited, as the required number of events has not yet been reached. We did this analysis to establish and compare adverse events and patient-reported symptoms and health-related quality of life in women with high-risk endometrial cancer treated in PORTEC-3.

METHODS

Study design and participants

PORTEC-3 was a multicentre, open-label, randomised intergroup trial led by the Dutch Gynaecological Oncology Group. Patients were enrolled in the study by the radiation oncologists from the participating centres in the following international participating groups: the Medical Research Council and the National Cancer Research Institute (UK), the Australia New Zealand Gynaecological Oncology Group (Australia and New Zealand), Mario Negri Gynecologic Oncology group (Italy), Fedegyn (France) and National Cancer Institute of Canada Clinical Trials Group (Canada).

Patients were eligible for inclusion in this trial if they had International Federation of Gynecology and Obstetrics 2009 categorised stage IA grade 3 endometrial carcinoma with myometrial invasion and with documented lymph-vascular space invasion; stage IB grade 3; stage II, stage IIIA, or IIIC (or IIIB if parametrial invasion only); serous or clear cell histology with stage IA (with invasion), IB, II, or III. Eligible patients also had to have adequate WHO performance scores (WHO score 0–2); bone marrow (white blood cell count ≥ 3.0 cells $\times 10^9$/L, platelets $\geq 100 \times 10^9$/L); liver function (bilirubin $\leq 1.5 \times$ upper limit of normal [ULN], aspartate aminotransferase concentration $\leq 2.5 \times$ ULN, or alanine aminotransferase concentration $\leq 2.5 \times$ ULN); and kidney function (creatinine clearance >60 mL/min calculated according to Cockroft[18] or >50 mL/min EDTA clearance) and be aged older than 18 years. Exclusion criteria were having uterine sarcoma, previous malignancy less than 10 years ago, receipt of previous pelvic radiotherapy, hormonal or chemotherapy, gross cervical involvement with radical hysterectomy, inflammatory bowel disease, residual macroscopic tumour, impaired renal or cardiac function, neuropathy grade 2 or worse, hearing impairment grade 3 or worse, or congenital hearing disorder.

Surgery comprised of total abdominal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy. Lymphadenectomy was left at the discretion of the participating centres. For serous or clear cell carcinoma, staging including omentectomy; peritoneal biopsies and lymph node sampling were recommended. Upfront central pathology review was undertaken by the reference gynaecological pathologists of the participating groups to confirm final eligibility for the study.

Written informed consent was obtained from all patients. The protocol was approved by the Dutch Cancer Society, and the ethics committees of the participating groups or centres. Participating groups obtained their institutional review board and ethics approvals and were funded by separate grants. The protocol is available online (www.clinicalresearch.nl/portec3).

Randomisation and masking

Patients were randomly allocated (1:1) to receive either chemoradiotherapy or radiotherapy alone. Treatment was allocated with a biased coin minimisation procedure, with stratification according to participating centre, lymphadenectomy (yes or no), stage, and histological type. The outcome of the allocation was computer generated and not predictable by the investigators. Patients were registered and randomised by the participating group's data centres and treatment was assigned with a web-based application. The trial number and assigned treatment were generated immediately by the randomisation programme and confirmed by email to the investigators. Participants and investigators were not masked to treatment allocation.

Procedures

Pelvic radiotherapy was given in both treatment groups (48.6 Gy in 1.8 Gy fractions, five times a week for 5.5 weeks). The clinical target volume included the proximal vagina, parametrial tissues, and internal, external, and common iliac lymph node regions up to the upper S1 level (the level of promontory). The clinical target volume was extended for lymph node involvement. In case of cervical involvement, a brachytherapy boost was given. Treatment had to be started preferably within 4–6 weeks after surgery, but no later than 8 weeks after surgery. Treatment breaks were avoided and could not exceed 2 days, overall treatment time for radiotherapy could not exceed 50 days.

Patients in the chemoradiotherapy group received two cycles of cisplatin 50 mg/m2 in the first and fourth week of radiotherapy, followed by four cycles of carboplatin area under the curve (AUC) 5 and paclitaxel 175 mg/m2 at 21-day intervals (and a 28-day interval between the second concurrent and first adjuvant cycle). This schedule was based on the RTOG9708 trial,[16] with substitution of cisplatin with carboplatin in the adjuvant phase. In the event of haematological, renal, or other toxicities, cisplatin was postponed for 1 week. If recovery required more than 1 week or in the case of neurological adverse events of grade 2 or worse, cisplatin was discontinued. Carboplatin was postponed or stopped in the case of severe haematological toxicity. Carboplatin dose was reduced to AUC 4 if recovery to grade 1 was attained at two weeks. Paclitaxel was postponed if grade 2 neuropathy was reported and stopped if recovery exceeded 1 week or grade 3 neuropathy developed. After recovery or reduction to grade 1 adverse events, paclitaxel dose was reduced to 135 mg/m2. Carboplatin and paclitaxel were delayed for other grade 3–4 toxicities, and discontinued if there was no recovery or reduction to grade 1 adverse events.

Patients were assessed every 3 months for the first 24 months, and every 6 months up to 5 years. Long-term outcome evaluation at 7 and 10 years was obtained, preferably by follow-up visits, or by information from their general practitioner. At each follow-up visit, a patient history with emphasis on treatment-related morbidity, and physical and pelvic

examination was done. Chest radiograph, blood count, and chemistry tests (including Ca-125) were obtained once a year, up to 5 years after randomisation.

Toxicity was graded with the Common Terminology Criteria for Adverse Events version 3.0 and was assessed at baseline (after surgery), completion of radiotherapy, at each chemotherapy cycle, and at 6-month follow-up intervals from randomisation until 5 years and at 7 and 10 years. Health-related quality of life questionnaires were completed at baseline after surgery and after completion of radiotherapy, at 6-month intervals from randomisation until 24 months, and at 36 and 60 months. Health-related quality of life was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30, version 3.0).[19] As the EORTC endometrial module was not yet available, the cervix 24 (CX24) module was used, with added chemotherapy and neuropathy subscales from the ovarian 28 (OV28) module.[20,21] Higher scores on functional and global health-related quality of life scales represented better levels of functioning. On the symptom subscales, higher scores reflected higher levels of symptoms.

All adverse events were graded and adverse events of grade 2 or worse were reported on case record forms, irrespective of the relation with study treatment. For mild (grade 1) toxicities, the patient-reported health-related quality of life symptoms were used. Serious adverse events were reported within 24 h, specifying adverse event grade and relation to study treatment. Time from randomization was used to compare severity and duration of toxicities between the treatment groups; importantly, the 6-month timepoint was about 1 month after completion of chemotherapy in the chemoradiotherapy group.

Outcomes

Primary endpoints were overall survival and failure-free survival, with failure defined as any relapse or death related to endometrial carcinoma. Secondary endpoints were treatment-related toxicity, health-related quality of life, and pelvic or distant relapse.

Statistical analysis

The PORTEC-3 trial was powered (80%) to detect a difference of 10% (HR 0.67) in 5-year overall survival (65% to 75%); for this, 198 events were required, and a minimum of 655 patients. The analysis plan for the second primary endpoint failure-free survival will be added in an amendment to the trial protocol. Primary and secondary outcomes not involving toxicity or health-related quality of life were analysed by intention to treat. Safety outcomes were assessed in all patients who received at least one cycle of chemotherapy and 1 week of radiotherapy (in the chemoradiotherapy group) and 1 week of radiotherapy (in the radiotherapy alone group). Although no specific power calculations were done for the toxicity and health-related quality of life analysis, the minimum

required number of 655 patients ensured sufficient power to detect clinically relevant differences. Toxicity and quality of life were analysed according to treatment received.

Formal tests for the differences in relapse and survival rates between the two groups were done with the Kaplan-Meier method, the log-rank test, and Cox regression analysis. The median follow-up of all patients was estimated by the inverse Kaplan-Meier method. We measured toxicity at baseline, at completion of radiotherapy, every cycle of concurrent and adjuvant chemotherapy, and 6, 12, 18, and 24 months; quality of life was measured at baseline, completion of radiotherapy, and 6, 12, 18, and 24 months after randomisation. During follow-up, toxicity and quality of life forms completed within a 3-month window before or after the designated timepoint were included. The time during treatment was defined as all toxicity forms related to radiotherapy and all cycles of concurrent and adjuvant chemotherapy.

Criteria to be removed from the analysis were ineligibility or withdrawal of informed consent before the start of treatment. Patients were evaluable for health-related quality of life analysis if they had completed baseline and at least one follow-up form. Missing data for patients were handled as missing-at-random, assuming that missing data was not related to the values of the unobserved variables. This is an assumption that is not possible to verify statistically.[22] The prevalence of toxicity graded according to the Common Terminology Criteria for Adverse Events version 3.0 was calculated at each timepoint. Per adverse event, the maximum grade per patient was calculated (worst ever by patient). The maximum grade over the entire course of therapy and follow-up for any adverse events and for the individual patient was used as a summary of toxicity. Fisher's Exact test was used to compare toxicity between the two treatment groups. A prespecified health-related quality of life analysis was done according to the EORTC Quality of Life Group guidelines.[23] Baseline scores of both treatment groups were compared with a *t* test, or Armitage trend test for single items. A linear mixed model was used to obtain estimates of the EORTC QLQ-C30, CX24, and OV28 subscales at each of the timepoints, with patient as random effect and time (categorical), treatment, and their interaction between time and treatment as fixed effects. Single items were analysed with (binary) logistic regression with random effect, combining scores of 1–2 ("not at all" and "a little") and 3–4 ("quite a bit" and "very much"). The difference in health-related quality of life between the groups over time was tested by a joint Wald test of all treatment-by-time interaction in the linear or logistic mixed model. To guard against false-positive results because of multiple testing, a two-sided p value of less than or equal to 0.01 was considered statistically significant.

Guidelines for the interpretation of clinically relevant changes to EORTC QLQ-C30 scores were applied.[24,25] For scales not included in the guidelines, changes were assessed according to Osoba and colleagues.[26] Statistical analyses were done with SPSS, version 20.0, and R statistical software, version 3.2.1.

A Data and Safety Monitoring Board oversaw the study. After discussion within the trial management group and with approval of the Data and Safety Monitoring Board, the decision was made to submit for publication. The study was closed on Dec 20, 2013, after achieving complete accrual; follow-up is continuing. This trial is registered with ISRCTN.com, number ISRCTN14387080, and with ClinicalTrials.gov, number NCT00411138.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The central data manager (KWV-A), the principal investigator (CLC) and associated investigators (SMdB, RAN), and trial statistician (HP) had full access to the data. The Dutch Cancer Society Scientific Review Board approved the trial design. The corresponding author and chief investigator had full access to all of the data and the final responsibility to submit for publication.

RESULTS

Between Sept 15, 2006, and Dec 20, 2013, we recruited 686 patients to the PORTEC-3 trial. Of these patients, 13 did not meet inclusion criteria (figure 1). Reasons for exclusion were different stage, macroscopic residual disease, low creatinine clearance, impaired hearing (≥grade 3), or different histological type. Another 13 patients withdrew their informed consent immediately after randomisation and were excluded from this analysis, leaving 660 patients (330 in each group) for intention-to-treat analysis. Seven (1%) of 660 patients refused the allocated treatment (five in the chemoradiotherapy group and two in the radiotherapy alone group) and switched to the other treatment group (figure 1). For analysis of toxicity and health-related quality of life these seven patients were assessed by treatment received, resulting in 327 patients in the chemoradiotherapy group and 333 patients in the radiotherapy alone group. Median follow-up at the time of analysis for all patients was 42.3 months (IQR 25.8–55.1); 42.1 months (25.7–54.7) in the chemoradiotherapy group and 42.4 months (27.1– 55.4) in the radiotherapy alone group. With ongoing follow-up, 487 (74%) patients (240 in the chemoradiotherapy group and 247 in the radiotherapy alone group) had reached the 2-year timepoint by the time of this analysis.
Patient characteristics were well balanced between the chemoradiotherapy and radiotherapy alone groups (table 1). Lymphadenectomy was performed in 203 (62%) in the chemoradiotherapy group and in 205 (62%) patients in the radiotherapy alone group. Radiotherapy was discontinued by one (<1%) patient who received chemoradiotherapy because of disease progression and by five (2%) patients who received radiotherapy alone because of toxicity (n=4) and an accidental fall with femur fracture (n=1). A brachytherapy boost was given in 149 (46%) of 327 patients in the chemoradio-

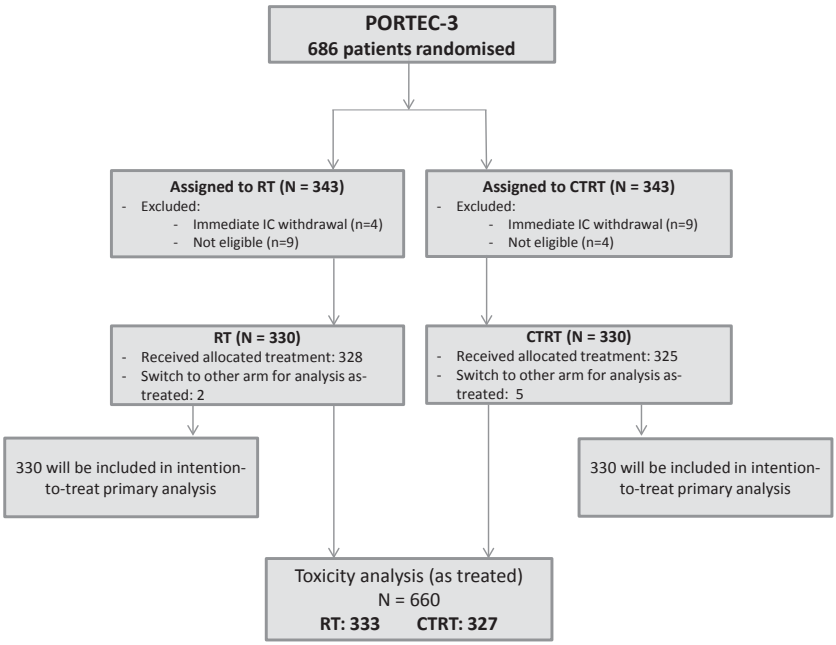

Figure 1. Trial profile

therapy group and 156 (47%) of 333 patients in the radiotherapy alone group. Treatment completion details are shown in table 1. Chemotherapy was discontinued in 61 (19%) patients because of drug-related toxicity in 31 (9%) patients, patient decision in 20 (6%) patients, disease progression in seven (2%) patients, or for other reasons in three (1%) patients. Dose reductions were reported if the dose was reduced by more than 10%. At least one dose reduction of cisplatin (to 40 mg/m2) was recorded for five (2%) patients, of carboplatin (from AUC 5 to AUC 4) for 22 (7%) patients, and of paclitaxel (from 175 mg/m2 to 135 mg/m2) for 34 patients (10%). Analysis of primary outcomes is ongoing and will be reported in a future publication.

For 570 (86%) of 660 patients, a baseline questionnaire and at least one follow-up questionnaire was received, 292 for the chemoradiotherapy group and 278 in the radiotherapy alone group. These 570 responders were assessable for health-related quality of life. 90 (14%) of 660 patients could not be assessed for health-related quality of life, mostly because of a missing form at baseline, whereas some questionnaires were invalid because of missing dates of completion or a completion date after the first day of radiotherapy. At 24 months, health-related quality of life scores of 364 (55%) patients had been received, which corresponds to 64% of the 570 responders: (194 [66%] of 292 patients in the chemoradiotherapy group and 170 [61%] of 278 patients in the radiotherapy alone group). Questionnaire response rates for each timepoint are given

Table 1. Characteristics of as-treated population by treatment group

	Chemoradiotherapy (n = 327)		Radiotherapy alone (n = 333)	
	No. of patients	%	No. of patients	%
Age at randomisation (years)				
Median	62.5		61.9	
Interquartile range	56.5 - 68.0		55.9 - 68.1	
< 60 years	125	38%	143	43%
60-69 years	143	44%	129	39%
≥70 years	58	18%	61	18%
Missing data*	1		0	
FIGO 2009-stage				
Stage I	95	30%	97	31%
Stage II	79	25%	88	28%
Stage III	144	45%	131	41%
Missing data*	9		17	
Histologic grade and type				
EEC Grade 1	44	14%	45	14%
EEC Grade 2	81	25%	80	24%
EEC Grade 3	102	32%	111	34%
Non-endometrioid	83	26%	77	23%
Mixed	13	4%	17	5%
Missing data*	4		3	
WHO performance				
0 - 1	319	98%	327	98%
≥2	5	2%	5	2%
Missing data*	3		1	
Comorbidity				
Diabetes	45	14%	36	11%
Hypertension	115	35%	105	32%
Cardiovascular	30	9%	20	6%
Type of surgery				
Total abdominal hysterectomy and bilateral salpingo-oopherectomy	82	25%	87	26%
Total abdominal hysterectomy and bilateral salpingo-oopherectomy plus lymph node dissection or full staging (lymph node dissection with omentectomy and peritoneal biopsies)	153	47%	146	44%
Total laparoscopic hysterectomy and bilateral salpingo-oopherectomy	41	13%	40	12%
Total laparoscopic hysterectomy and bilateral salpingo-oopherectomy plus lymph node dissection or full staging (lymph node dissection with omentectomy and peritoneal biopsies)	50	15%	59	18%
Missing data*	1		1	

Table 1. Characteristics of as-treated population by treatment group (*continued*)

	Chemoradiotherapy (n = 327)		Radiotherapy alone (n = 333)	
	No. of patients	%	No. of patients	%
Treatment completion				
Radiotherapy	326 (100%)		328 (98%)	
Brachytherapy boost	149 (46%)		156 (47%)	
1 cycle Cisplatin	325 (99%)		-	
2 cycles Cisplatin	305 (93%)		-	
1 cycle Carboplatin/Paclitaxel	303 (93%) / 303 (93%)		-	
2 cycles Carboplatin/Paclitaxel	295 (90%) / 295 (90%)		-	
3 cycles Carboplatin/Paclitaxel	279 (85%) / 267 (82%)		-	
4 cycles Carboplatin/Paclitaxel	262 (80%) / 235 (72%)		-	

Data are median (IQR) or n (%). *Missing values are not included in the percentage calculation. FIGO=International Federation of Gynaecology and Obstetrics. EEC=endometrioid endometrial carcinoma.

Table 2. Toxicity reported by physicians using the CTCAE v3.0 during treatment and follow-up.

	Maximum grade per patient during treatment CTRT n=327; RT n=326					
	Grade 2			Grade 3-4		
	CTRT n (%)	RT n (%)	p*	CTRT n (%)	RT n (%)	p#
Any	111 (34)	102 (31)	<0.0001	198 (61)	42 (13)	<0.0001
Any grade 3	na	na		149 (46)	42 (13)	
Any grade 4	na	na		49 (15)	0 (0)	
Auditory/hearing	14 (4)	3 (1)	0.011	1 (<1)	1 (<1)	
Fatigue	70 (21)	7 (2)	<0.0001	10 (3)	0 (0)	0.0018
Alopecia	185 (57)	1 (<1)	<0.0001	na	na	
Any gastrointestinal	145 (44)	79 (24)	<0.0001	47 (14)	18 (6)	0.0002
Diarrhea	103 (31)	69 (21)	<0.0001	35 (11)	13 (4)	0.0014
Ileus/obstruction	3 (1)	5 (2)		2 (1)	2 (1)	
Nausea	68 (21)	24 (7)	<0.0001	9 (3)	2 (1)	0.063
Any haematological	99 (30)	19 (6)	<0.0001	148 (45)	18 (6)	<0.0001
Febrile neutropenia	na	na		9 (3)	1 (<1)	0.021
Infection with neutropenia	3 (1)	0 (0)	0.0018	7 (2)	0 (0)	0.015
Infection without neutropenia	21 (6)	1 (<1)	<0.0001	12 (4)	0 (0)	0.0004
Any neuropathy	78 (24)	1 (<1)	<0.0001	23 (7)	0 (0)	<0.0001
Motor neuropathy	13 (4)	1 (<1)	0.0001	4 (1)	0 (0)	
Sensory neuropathy	75 (23)	0 (0)	<0.0001	22 (7)	0 (0)	<0.0001
Any pain	101 (31)	23 (7)	<0.0001	31 (9)	4 (1)	<0.0001
Genitourinary incontinence	11 (3)	5 (2)		1 (<1)	0 (0)	
Genitourinary urinary frequency	22 (7)	10 (3)	0.041	2 (1)	2 (1)	
Thrombosis or embolism	2 (1)	0 (0)	0.031	4 (1)	0 (0)	

AE were calculated at each time point. Per AE, the maximum grade per patient was calculated (worst ever by patient). p* = significant level < 0.01 for grade 2, 3 and 4; p# = significant level <0.01 for grade 3 and 4. Only p-values ≤0.10 were listed.

in the appendix (Table S1). WHO performance score was different between those who responded to the questionnaire and those who did not, with WHO 0–1 recorded in 565 (99%) of 570 patients who responded versus 85 (94%) of 90 patients who did not respond, and WHO score of 2 or more in five (1%) patients who responded versus five (6%) patients who did not respond (p=0.007). No other differences were seen in patient characteristics between responders and non-responders (data not shown). 89% of the responders completed all items of the EORTC QLQ-C30 in the returned questionnaires, 80% completed all items of the CX24 subscale, 92% completed all non-sexual items, and 91% of the responders completed all items of the OV28 subscale.

Adverse event incidence during and after treatment is summarised in table 2. A comprehensive list of adverse events is provided in the appendix (Table S3). At baseline, no significant differences in adverse events were recorded between groups. Baseline grade 2 adverse events were reported for 109 (33%) of 327 patients who received chemoradiotherapy and 93 (29%) of 326 patients who received radiotherapy alone, and grade 3–4

Maximum grade per patient at 6 months CTRT n=327; RT n=324						Maximum grade per patient at 12 months CTRT n=305; RT n=304					
Grade 2			Grade 3-4			Grade 2			Grade 3-4		
CTRT	RT	p*	CTRT	RT	p#	CTRT	RT	p*	CTRT	RT	p#
n (%)	n (%)		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
128 (39)	95 (29)	<0.0001	55 (17)	25 (8)	0.0005	102 (33)	87 (29)	0.058	33 (11)	22 (7)	
na	na		49 (15)	21 (6)		na	na		28 (9)	20 (7)	
na	na		6 (2)	4 (1)		na	na		5 (2)	2 (1)	
8 (2)	3 (1)		0 (0)	0 (0)		10 (3)	2 (1)	0.037	0 (0)	0 (0)	
9 (3)	2 (1)	0.055	1 (<1)	1 (<1)		5 (2)	4 (1)		0 (0)	2 (1)	
64 (20)	0 (0)	<0.0001	na	na		0 (0)	2 (1)		na	na	
19 (6)	17 (5)		7 (2)	9 (3)		21 (7)	19 (6)		7 (2)	2 (1)	
8 (2)	11 (3)	0.1	0 (0)	3 (1)		11 (4)	8 (3)		1 (<1)	1 (<1)	
1 (0)	1 (0)		7 (2)	8 (2)		2 (1)	3 (1)		4 (1)	2 (1)	
7 (2)	5 (2)		5 (2)	2 (1)		3 (1)	2 (1)		1 (0)	0 (0)	
54 (17)	27 (8)	<0.0001	24 (7)	6 (2)	0.001	26 (9)	20 (7)		4 (1)	7 (2)	
na	na		0 (0)	0 (0)		na	na		0 (0)	0 (0)	
0 (0)	0 (0)		1 (<1)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
5 (2)	1 (<1)		0 (0)	0 (0)		1 (<1)	3 (1)		1 (<1)	0 (0)	
42 (13)	1 (<1)	<0.0001	8 (2)	2 (1)		26 (9)	2 (1)	<0.0001	4 (1)	1 (<1)	
7 (2)	1 (<1)	0.089	3 (1)	2 (1)		1 (0)	0 (0)		3 (1)	1 (<1)	
42 (13)	0 (0)	<0.0001	6 (2)	0 (0)	0.031	26 (9)	2 (1)	<0.0001	4 (1)	1 (<1)	
31 (9)	30 (9)		3 (1)	7 (2)		27 (9)	21 (7)		8 (3)	4 (1)	
6 (2)	7 (2)		1 (<1)	0 (0)		8 (3)	9 (3)		1 (<1)	1 (<1)	
5 (2)	6 (2)		0 (0)	0 (0)		4 (1)	8 (3)		0 (0)	1 (<1)	
3 (1)	0 (0)		2 (1)	1 (<1)		1 (<1)	0 (0)		0 (0)	1 (<1)	

toxicities were reported in 33 (10%) patients who received chemoradiotherapy and 28 (9%) patients who received radiotherapy alone. No deaths occurred during treatment; two patients (one in each group) died shortly after treatment: one patient in the chemoradiotherapy group died from pneumonia after surgery for bowel obstruction because of adhesions; one elderly patient in the radiotherapy alone group died 3 weeks after radiotherapy because of pneumonia and subsequent multiorgan failure. The death of both patients was not related to the study treatment as reported by the treating physician.

During the study, including whole treatment and follow-up period, 89 (27%) of 327 patients in the chemoradiotherapy group versus 154 (47%) of 326 patients in the radiotherapy alone group had a maximum toxicity of grade 2 adverse events. Grade 3 adverse events or worse were reported for 229 (70%) of 327 patients in the chemoradiotherapy group versus 112 (34%) of 326 patients in the radiotherapy alone group (figure 2). During treatment, grade 2 or worse adverse events were found in 309 (94%) of 327 patients in the chemoradiotherapy group versus 145 (44%) of 326 patients in the radiotherapy alone group ($p<0.0001$); grade 3 or higher were found in 198 (61%) patients in the chemoradiotherapy group versus 42 (13%) patients in the radiotherapy alone group ($p<0.0001$; figure 2, table 2). Most grade 3 or worse toxicities in both groups during treatment were haematological, gastrointestinal, or pain related. During treatment, grade 3 or worse sensory neuropathy was reported in 22 (7%) patients and motor neuropathy was reported in four (1%) patients, all in the chemo radiotherapy group. At 12 and 24 months after treatment, no significant difference in grade 3 or worse adverse events was seen between the groups.

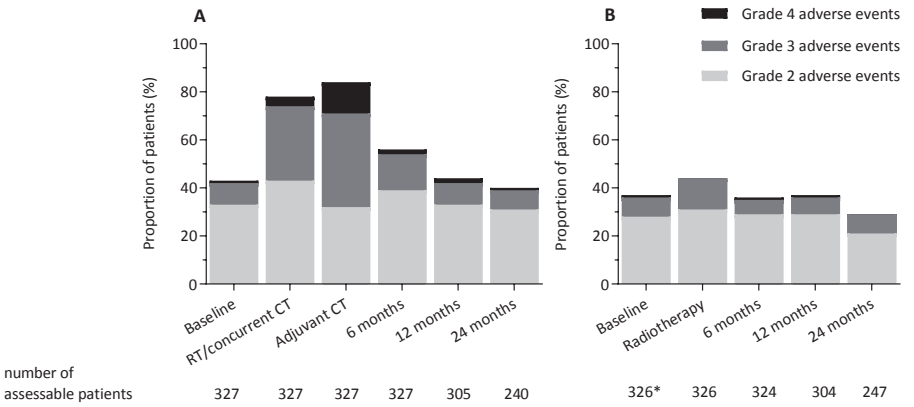

Figure 2. Incidence of the maximum physician-reported adverse event grades per patient for each timepoint at baseline, during treatment and at 6, 12, and 24 months follow-up in the chemoradiotherapy group (A) and the radiotherapy alone group (B)

*Total not 333 because of missing forms.

The most important persisting toxicity was grade 2 or worse sensory neuropathy at 12 months in 30 (10%) patients in the chemoradiotherapy group versus three (1%) patients in the radiotherapy group, and 25 (10%) patients in the chemoradiotherapy group versus one (<1%) patient in the radiotherapy alone group at 24 months (p<0.0001). No significant differences in gastrointestinal, genitourinary, or haematological toxicities were seen at 12 and 24 months. Slightly worse auditory toxicity and bone-related pain were found in patients treated with chemoradiotherapy at 12 months (appendix Table S3).

Results of the EORTC QLQ-C30 functioning subscales and global health status, and mean scores for CX24 and OV28 subscales are summarised in table 3. All single symptom items are reported in appendix (Table S4). During treatment, patients treated with chemoradiotherapy scored significantly lower on most EORTC functioning scales; 10–20-point lower scores on physical, role, and social functioning, and global health status compared with patients treated with radiotherapy alone. However, rapid recovery was reported,

Table 3. Patient- reported health -related quality of life symptoms using the EORTC QLQ-C30 and subscales of CX-24 en OV-28 over the treatment and two-year follow up

	Questionnaire time points						p-value		
			Months						
	Baseline	After RT	6	12	18	24	Changes over time	Difference between groups	Differences between groups over time
EORTC functioning scales									
Physical functioning									
Chemoradiotherapy	81.3	76.3	72.5	80.1	79.5	80.0	<0.0001	<0.0001	<0.0001
Radiotherapy	84.6	83.1	86.5	85.9	84.8	85.5			
Role functioning									
Chemoradiotherapy	70.4	66.5	67.8	79.3	78.7	79.8	<0.0001	<0.0001	<0.0001
Radiotherapy	73.7	74.5	84.7	85.1	83.7	85.8			
Emotional functioning									
Chemoradiotherapy	74.4	76.9	77.1	79.1	80.3	81.1	<0.0001	0.21	0.74
Radiotherapy	77.6	81.7	80.6	82.2	82.0	84.7			
Cognitive functioning									
Chemoradiotherapy	87.0	81.8	79.8	84.5	82.8	85.1	<0.0001	0.002	0.008
Radiotherapy	88.0	85.6	86.9	86.8	86.2	85.7			
Social functioning									
Chemoradiotherapy	78.1	73.5	74.4	84.2	85.4	85.4	<0.0001	<0.0001	<0.0001
Radiotherapy	80.4	78.7	88.3	89.0	87.7	91.2			
Global health status/ Quality of Life									
Chemoradiotherapy	86.2	77.3	81.8	89.8	87.3	89.6	<0.0001	<0.0001	<0.0001
Radiotherapy	87.1	85.3	89.6	90.1	90.7	90.5			

Table 3. Patient- reported health -related quality of life symptoms using the EORTC QLQ-C30 and subscales of CX-24 en OV-28 over the treatment and two-year follow up (continued)

	Questionnaire time points						p-value		
			Months						
	Baseline	After RT	6	12	18	24	Changes over time	Difference between groups	Differences between groups over time
EORTC symptom scales									
Fatigue									
Chemoradiotherapy	28.9	42.0	38.4	27.7	28.9	26.9	<0.0001	<0.0001	<0.0001
Radiotherapy	26.5	34.1	23.7	23.7	22.7	22.5			
Nausea and vomiting									
Chemoradiotherapy	3.8	14.1	8.8	4.7	3.8	3.5	<0.0001	<0.0001	<0.0001
Radiotherapy	4.0	10.0	5.5	6.9	4.8	6.7			
Pain									
Chemoradiotherapy	18.4	21.2	23.3	20.8	19.9	19.0	0.06	0.09	0.24
Radiotherapy	17.0	19.6	16.6	16.6	16.0	16.7			
CX 24 subscales									
Symptom experience*									
Chemoradiotherapy	9.6	16.2	12.1	11.6	11.9	11.7	<0.0001	0.66	0.55
Radiotherapy	9.5	16.8	12.1	12.6	11.1	11.9			
Body image									
Chemoradiotherapy	11.6	16.6	24.9	16.0	15.0	15.6	<0.0001	<0.0001	<0.0001
Radiotherapy	9.9	12.8	12.7	12.4	11.6	11.2			
Sexual functioning†									
Chemoradiotherapy	13.2	22.3	18.3	19.9	17.2	21.4	0.05	0.36	0.34
Radiotherapy	9.5	22.4	22.0	23.6	22.7	25.5			
OV 28 subscales									
Chemotherapy‡									
Chemoradiotherapy	7.9	18.7	31.2	14.7	14.0	13.2	<0.0001	<0.0001	<0.0001
Radiotherapy	6.2	11.2	12.1	12.5	12.3	11.5			
Peripheral neuropathy									
Chemoradiotherapy	5.5	14.2	47.0	31.4	28.5	27.8	<0.0001	<0.0001	<0.0001
Radiotherapy	5.5	8.8	12.8	12.9	12.6	13.2			

All subscales responses were converted to 0 to 100 scales (according to the EORTC guidelines). Higher scores for functioning items and global quality of life scale represent a better level of functioning. For the symptom scales, a higher score refl ects a higher level of symptoms. EORTC QLQ-C30=European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. CX24=cervix 24. OV28=ovarian 28. *Subscale symptom experience included abdominal cramps, controlling bowels, blood in stool, urinary frequency, dysuria, urinary incontinence, diffi culty emptying bladder, lower back pain, vaginal irritation or soreness, vaginal discharge, and abnormal vaginal bleeding. †Responses to the questions of this subscale were only expected if the respondent was indicated to be sexually active. ‡Subscale chemotherapy included hair loss, taste change, muscle aches or pains, hearing problems, urinary frequency, or skin problems.

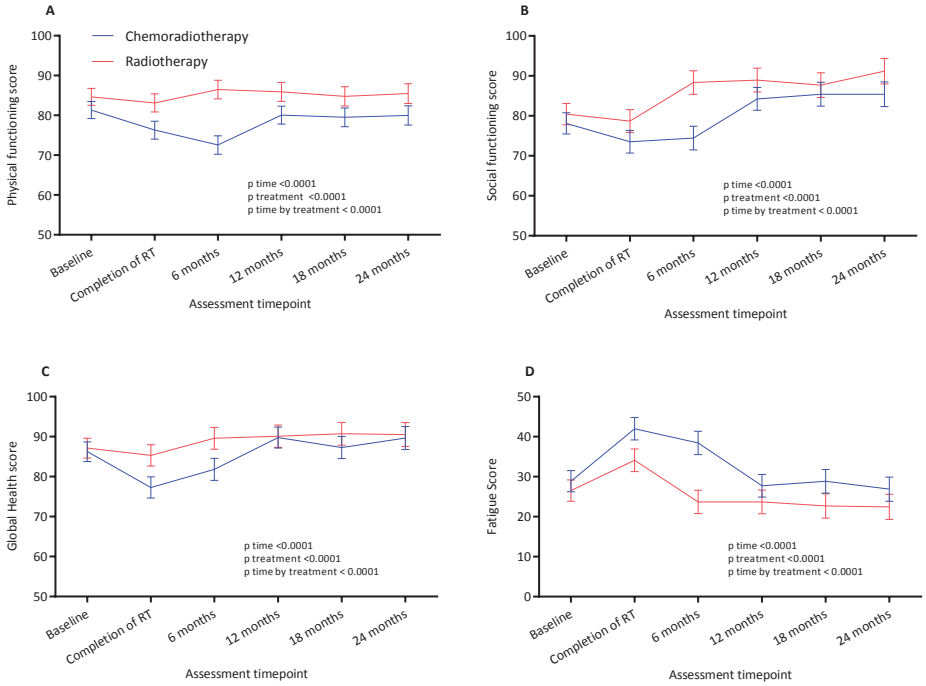

Figure 3. Patient functioning subscales and single-item symptom EORTC QLQ-C30 scores for physical functioning (A), social functioning (B), global health status or quality of life (C), and fatigue (D).
For physical functioning, social functioning, and global health status or quality of life, a higher score indicated a higher level of functioning or activity, and for fatigue, a higher score indicates a higher level of symptoms. Error bars show 95% CI. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. p time=difference in quality of life scores over time within the whole treatment group. p treatment=difference between the two treatment groups. p time by treatment=difference between the two treatment groups over time.

and at 12 months physical functioning was the only significant difference between the two treatment groups (figure 3).

The most frequently reported severe ("quite a bit" or "very much") symptoms at 6 months were tingling or numbness in 111 (52%) of 214 patients in the chemoradiotherapy group versus 15 (7%) of 209 patients in the radiotherapy alone group ($p<0.0001$), muscle or joint pain in 80 (37%) of 214 patients in the chemoradiotherapy group versus 45 (22%) of 207 patients in the radiotherapy alone group ($p=0.002$), fatigue in 66 (31%) of 210 patients versus 36 (17%) patients ($p=0.0004$), weakness in the arms or legs in 76 (36%) of 214 patients versus 24 (11%) of 209 patients ($p<0.0001$), and hair loss in 88 (44%) of 200 patients versus eight (4%) of 208 patients ($p<0.0001$), with events in the chemoradiotherapy group significantly higher in all these cases. At 24 months, most differences had subsided and the most frequent symptoms did not differ much from baseline (figure 4).

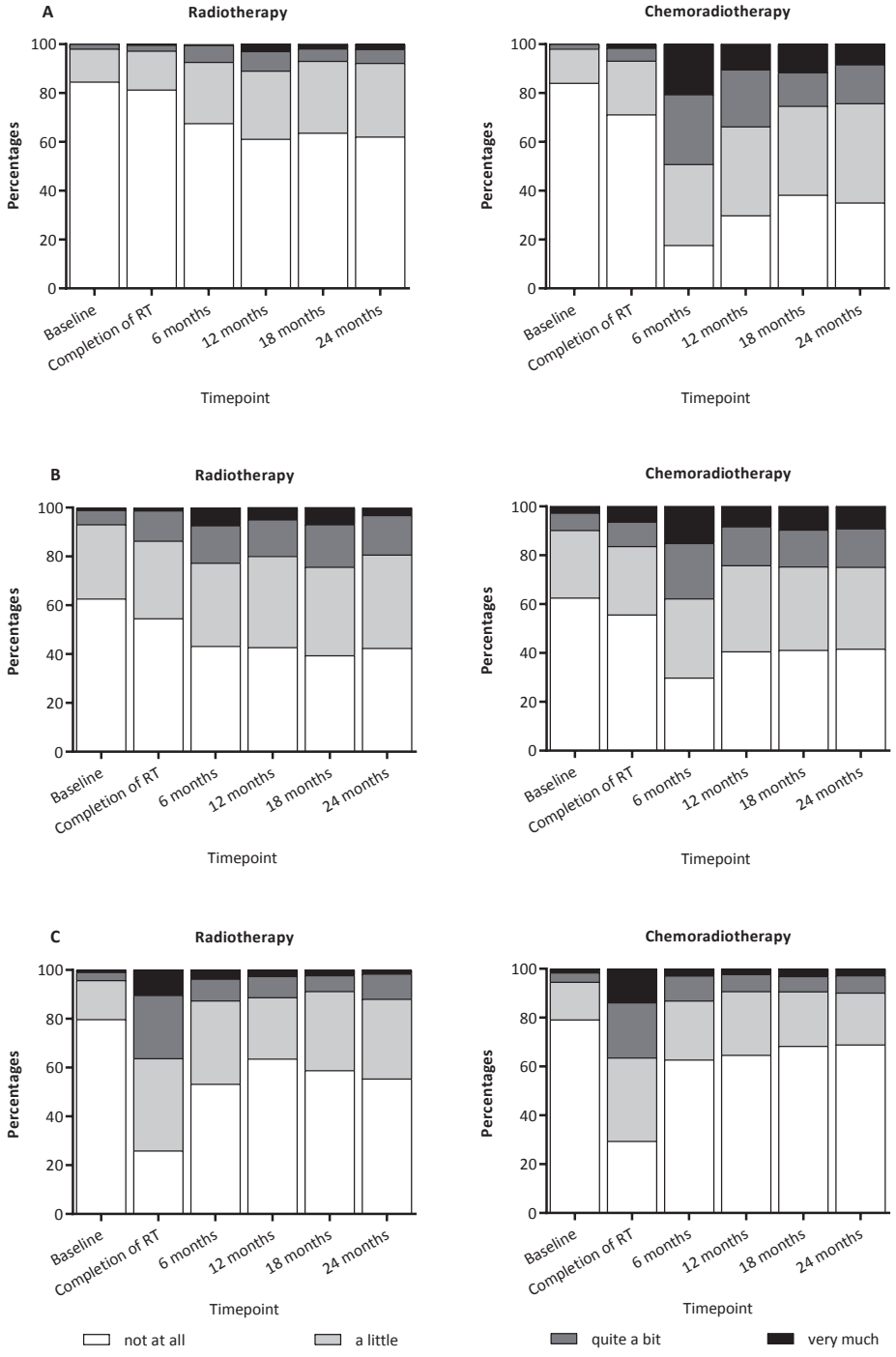

Figure 4. Patient responses on single-item symptom scales over time for tingling or numbness (A), muscle or joint pain (B), and diarrhoea (C) in the chemoradiotherapy group and the radiotherapy alone group

Tingling or numbness was still significantly higher in patients in the chemoradiotherapy group (48 [25%] of 194 *vs* 11 [6%] of 170 patients; p<0.0001).
Patient-reported lymphoedema did not differ between the two treatment groups (appendix Table S4). Severe lymphoedema was reported more frequently by patients who had undergone a lymphadenectomy (both treatment groups combined): 47 (17%) of 276 patients after lymphadenectomy versus 13 (8%) of 163 patients without lymphadenectomy at 12 months (p=0.01) and 38 (16%) of 237 patients versus 14 (11%) of 127 patients at 24 months (p=0.2). After lymphadenectomy, severe lymphoedema was reported by 18 (15%) of 120 patients in the chemoradiotherapy group and 20 (17%) of 117 patients in the radiotherapy alone group at 24 months (p=0.84), compared with seven (10%) of 69 patients and seven (12%) of 58 patients, respectively, who had no lymphadenectomy (p=0.69; appendix, Figure S2).
No significant differences in sexual functioning score were seen between the treatment groups, measured according to CX24 (table 3). Sexual activity was low in both groups, but was slightly higher in the radiotherapy alone group during treatment (p=0.006), and similar thereafter (see appendix Table S4).

DISCUSSION

This analysis of toxicity and 2-year health-related quality of life in the PORTEC-3 trial for women with high-risk endometrial cancer clearly shows that adjuvant chemotherapy given during and after pelvic radiotherapy causes significantly higher incidence of severe adverse events and of patient-reported symptoms, and a decreased level of patient functioning and health-related quality of life compared with radiotherapy alone. However, rapid recovery was seen, with reduction of all incidence and grades of adverse events between 6 and 12 months after randomisation, and without significant differences in grade 3 or worse adverse events at 12 and 24 months. The only remaining significant difference in adverse events at 12 and 24 months was increased grade 2 or worse sensory neuropathy in the chemoradiotherapy group compared with the radiotherapy alone group (25 [10%] of 240 *vs* 1 [<1%] of 247), with health-related quality of life showing "quite a bit" or "very much" tingling or numbness reported by 25% of patients in the chemoradiotherapy group versus 6% of patients in the radiotherapy alone group. After 24 months, patients treated with chemoradiotherapy group still had slightly lower physical functioning scores, which might partly be because of their higher rate of peripheral neuropathy. Most functioning scores showed small remaining differences (0–6 points) in mean scores, which are of borderline clinical relevance according to the guidelines for interpretation of the EORTC QLQ-C30.[24,25]

Patients treated in the chemoradiotherapy group reported significantly more tingling or numbness, muscle or joint pain, fatigue, weakness in the arms and legs, and hair loss at 6 months. All of these items, together with a longer treatment duration and more intense treatment because of the chemotherapy could be contributing to lower quality of life scores. The association between individual symptoms and overall quality of life will be a subject of further investigation.

The 6-month timepoint when most severe adverse events and worst quality of life were reported by patients receiving chemoradiotherapy was only 1 month after completion of chemotherapy, whereas patients treated with radiotherapy alone already had 4 months of recovery time. These results represent the toxicity profiles of the patients in the two treatment groups and provide a realistic view of the time with toxicity in the chemoradiotherapy group, which is of relevance for patient counselling when considering chemotherapy.

Data for the toxicity of chemotherapy in advanced or metastatic endometrial cancer are mainly available from the randomised trials[27] in which doxorubicin and cisplatin with or without paclitaxel were used. Incidence of sensory neuropathy in those trials during chemotherapy was significantly higher than in the PORTEC-3 trial, with 27% of patients having grade 2 adverse events and 12% of patients having grade 3 neuropathy when treated with the doxorubicin, cisplatin, and paclitaxel triplet combination. Results of the randomised GOG-209[28] trial in which the triplet chemotherapy was compared with carboplatin-paclitaxel are pending, but an abstract reported similar efficacy with a better toxicity profile of carboplatin-paclitaxel (NCT00063999). The GOG-249 trial[29] compared pelvic radiotherapy alone with vaginal brachytherapy followed by three cycles of carboplatin and paclitaxel in patients with stage I–II endometrial cancer with high-intermediate-risk or high-risk features. First results at a median follow-up of 24 months showed no differences in recurrence-free and overall survival, with more acute toxicity in the chemotherapy group. Data for health-related quality of life are pending.

Data for toxicity and health-related quality of life of women treated with carboplatin or paclitaxel chemotherapy are mainly available from first-line therapy in ovarian cancer trials. Comparison is relevant, as patients with ovarian cancer are of similar age and have also had previous pelvic surgery, and the combination of radiation and chemotherapy was expected to be more toxic than chemotherapy alone. Ovarian cancer trials with a 3-weekly schema of carboplatin AUC6 and paclitaxel 175–180 mg/mL reported mainly grade 3–4 haematological toxicities, with similar grades of haematological toxicity and febrile neutropenia in the MITO-7 trial[30] compared with PORTEC-3, and higher grades reported in the JGOG-3016 trial.[31] Additionally with this 3-weekly schema, grade 3–4 sensory and motor neuropathy were reported in 6% and 4% respectively in JGOG 3016, compared with 7% and 1% in PORTEC-3, and 3% had any grade 3–4 neuropathy in the MITO-7 trial.

At 24 months after randomisation, patient-reported sensory neuropathy remained significantly worse in the chemoradiotherapy group than in the radiotherapy alone group. A population-based study in ovarian cancer survivors reported peripheral neuropathy (as measured with EORTC-OV28) in 51% of patients treated with chemotherapy versus 27% of participants treated without chemotherapy.[32] Neuropathy is a common symptom in the general population, increasing with age and with the prevalence of diabetes.[33] Women with higher levels of neuropathy reported lower levels of functioning and quality of life, and more fatigue.[32]

Completion rates for chemotherapy were 93% for cisplatin, 80% for carboplatin, and 72% for paclitaxel, with dose reductions in 7% of carboplatin and 10% of paclitaxel cycles. Completion was lower than in RTOG9708,[16] but reflects clinical practice in a large multicentre trial. In MITO-7,[30] 90% of the patients treated carboplatin-paclitaxel received all six cycles; but with dose reductions in 36%. No significant differences were seen between the treatment groups in sexual functioning. Similar to health-related quality of life findings in the PORTEC-1 and PORTEC-2 trials, baseline sexual activity just after surgery and during treatment was low, with improvement over time, but sexual activity in this elderly patient group remained lower compared with population data.[6]

The current endometrial cancer module (EN24) was not yet available when the PORTEC-3 trial was designed. Therefore the CX24 module has been used with the subscale of chemotherapy from OV28, which has not been specifically tested for endometrial cancer. This could be a possible limitation to the study, although the EN24 module is very similar to CX24, with some of the same chemotherapy-related questions as in OV28 included.[34]

PORTEC-3 assessed both physician-reported and patient-reported toxicities. Limited agreement between patient and physician reported scoring of toxicities has been shown, with significant physician under-reporting of lower grade toxicities.[35] In the PORTEC-3 study, physicians were required to report grade 2 or worse adverse events to focus on more severe toxicities, and patient-reported outcomes were used for mild toxicities. Although patient-reported and physician-reported symptoms use different scales, similar trends in types of symptoms over time were seen.

Both the PORTEC-3 trial and the GOG-258 trial used the same combined chemotherapy–radiotherapy schedule, but in comparison with radiotherapy alone and chemotherapy alone, respectively. The toxicity and health-related quality of life outcomes need to be considered in the light of final survival data. If these trials were to show the combined treatment to be superior, future trials should focus on treatment schedules with least toxicity. For ovarian cancer, several trials have been done to compare different (weekly) infusion schedules to achieve a balance between optimum therapy and acceptable toxicity.[30,31]

Overall, combined adjuvant chemotherapy and radiotherapy for high-risk endometrial cancer caused significantly higher incidence of severe adverse events and reduced

health-related quality of life during and after treatment compared with radiotherapy alone, but with rapid recovery. The most persisting and troublesome symptom was sensory neuropathy, rated as "quite a bit" or "very much" by 25% of patients at 24 months. This schedule of combined chemotherapy and radiotherapy is feasible, and these data are essential for patient counselling and shared decision making on adjuvant chemotherapy. The question remains whether the impact in terms of toxicities will be outweighed by an overall or failure-free survival benefit. Final analysis of the PORTEC-3 and GOG258 trials are awaited, to determine the benefit of chemoradiotherapy in women with high-risk endometrial cancer.

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SUPPLEMENTARY MATERIAL

Table S1. Questionnaire response rates during follow up

		Questionnaire time point					
		Months					
		Baseline	**After RT**	**6**	**12**	**18**	**24**
Responders	Chemoradiotherapy (n)	292	231	215	234	210	194
	Radiotherapy (n)	278	229	218	206	196	170
	Total (n)	570	460	433	440	406	364
Non responders	Missing at baseline (n)	90	90	90	90	90	90
	Response rate (%)	86%	70%	66%	67%	62%	55%

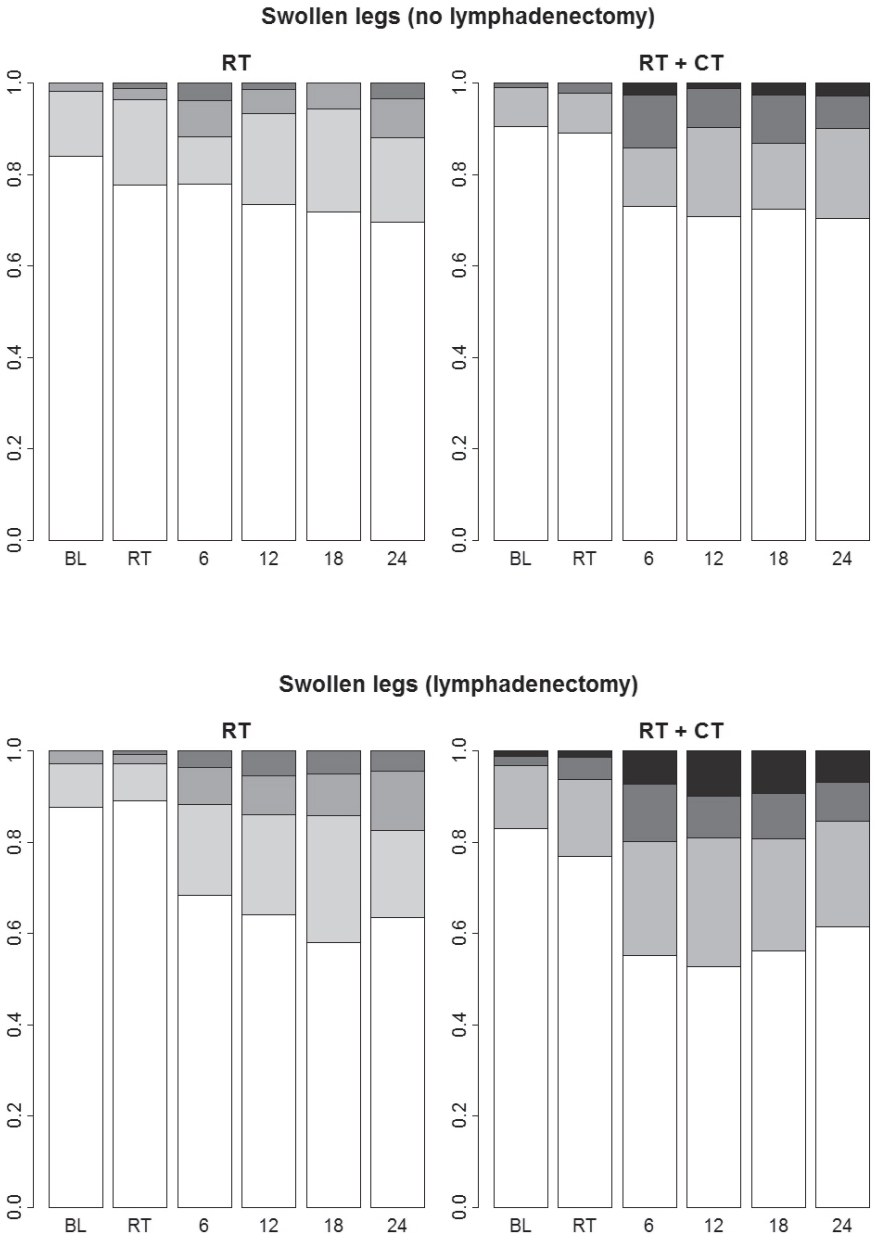


Figure S2. Patient reported swollen legs by lymphadenectomy and by treatment arm.
White bar represents % of patients rating the symptom 'not at all', light colour 'a little', more colour 'quite a bit' and darkest colour 'very much'. BL = baseline; RT = at completion of RT (with or without chemotherapy); 6 = 6 months; 12 = 12 months; 18 = 18 months; 24 = 24 months after randomisation. Abbreviations: RT, radiation therapy; CTRT, combined chemotherapy and radiation therapy.

Tabel S3. Toxicity reported by physicians using the CTCAE v3.0 during treatment and follow-up.

	Maximum grade per patient during treatment CTRT n=327; RT n=326					
	Grade 2		Grade 3		Grade 4	
	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)
Any	111 (34)	102 (31)	149 (46)	42 (13)	49 (15)	0 (0)
Allergic reaction						
Allergic reaction/ hypersensitivity	23 (7)	1 (0)	5 (2)	0 (0)	1 (0)	0 (0)
Auditory/hearing						
Auditory/hearing	14 (4)	3 (1)	1 (0)	1 (0)	0 (0)	0 (0)
Cardiac (general)						
Edema	7 (2)	2 (1)	1 (0)	0 (0)	0 (0)	0 (0)
Hypertension	19 (6)	12 (4)	6 (2)	3 (1)	0 (0)	0 (0)
Cardiac ischemia/infarction	1 (0)	0 (0)	1 (0)	0 (0)	1 (0)	0 (0)
Cardiac left ventricular failure	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Cardiovascular general - other	2 (1)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Cardiac arrythmia	4 (1)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Constitutional syptoms						
Fatigue	70 (21)	7 (2)	10 (3)	0 (0)	0 (0)	0 (0)
Other	28 (9)	2 (1)	1 (0)	0 (0)	2 (1)	0 (0)
Dermatology/skin						
Alopecia	185 (57)	1 (0)	na	na	na	na
Radiation dermatitis	18 (6)	5 (2)	1 (0)	1 (0)	0 (0)	0 (0)
Dermatology, wound complication (non-infectious)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Other	6 (2)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Endocrine						
Pancreatic - glucose intolerance	4 (1)	1 (0)	2 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal						
Any	145 (44)	79 (24)	47 (14)	18 (6)	0 (0)	0 (0)
Anorexia	31 (9)	9 (3)	3 (1)	4 (1)	0 (0)	0 (0)
Constipation	31 (9)	6 (2)	1 (0)	0 (0)	0 (0)	0 (0)
Dehydration	7 (2)	4 (1)	8 (2)	3 (1)	0 (0)	0 (0)
Diarrhea	103 (31)	69 (21)	35 (11)	13 (4)	0 (0)	0 (0)
Fistula	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Ileus/obstruction	3 (1)	5 (2)	2 (1)	2 (1)	0 (0)	0 (0)
Nausea	68 (21)	24 (7)	9 (3)	2 (1)	0 (0)	0 (0)
Proctitis	10 (3)	9 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Stomatitis / pharyngitis	6 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vomiting	31 (9)	9 (3)	5 (2)	0 (0)	0 (0)	0 (0)
Other	22 (7)	5 (2)	2 (1)	0 (0)	0 (0)	0 (0)
Hematological						
Any	99 (30)	19 (6)	108 (33)	18 (6)	40 (12)	0 (0)
Hemoglobin	104 (32)	0 (0)	27 (8)	0 (0)	0 (0)	0 (0)
Leucocytes/ WBC	93 (28)	3 (1)	59 (18)	1 (0)	17 (5)	0 (0)
Lymphocytes	50 (15)	16 (5)	98 (30)	17 (5)	10 (3)	0 (0)
Neutrophils/ granulocytes	60 (18)	1 (0)	38 (12)	1 (0)	28 (9)	0 (0)
Platelets	22 (7)	0 (0)	13 (4)	0 (0)	5 (2)	0 (0)

Maximum grade per patient at 6 months CTRT n=327; RT n=324						Maximum grade per patient at12 months CTRT n=305; RT n=304					
Grade 2		Grade 3		Grade 4		Grade 2		Grade 3		Grade 4	
CTRT n (%)	RT n (%)	CTRT (n (%)	RT n (%)	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)
128 (39)	95 (29)	49 (15)	21 (6)	6 (2)	4 (1)	102 (33)	87 (29)	28 (9)	20 (7)	4 (1)	2 (1)
2 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
8 (2)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	10 (3)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)
3 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
16 (5)	18 (6)	5 (2)	5 (2)	0 (0)	0 (0)	14 (5)	17 (6)	4 (1)	5 (2)	0 (0)	0 (0)
0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)
1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
9 (3)	2 (1)	1 (0)	1 (0)	0 (0)	0 (0)	5 (2)	4 (1)	0 (0)	2 (1)	0 (0)	0 (0)
5 (2)	3 (1)	0 (0)	0 (0)	1 (0)	0 (0)	5 (2)	4 (1)	0 (0)	0 (0)	1 (0)	0 (0)
64 (20)	0 (0)	na	na	na	na	0 (0)	2 (1)	na	na	na	na
1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2 (1)	2 (1)	4 (1)	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)	3 (1)	0 (0)	0 (0)	0 (0)
19 (6)	17 (5)	6 (2)	7 (2)	1 (0)	2 (1)	21 (7)	19 (6)	5 (2)	2 (1)	2 (1)	0 (0)
2 (1)	4 (1)	2 (1)	2 (1)	0 (0)	0 (0)	4 (1)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)
7 (2)	3 (1)	1 (0)	2 (1)	0 (0)	0 (0)	8 (3)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)
0 (0)	2 (1)	3 (1)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
8 (2)	11 (3)	0 (0)	3 (1)	0 (0)	0 (0)	11 (4)	8 (3)	1 (0)	1 (0)	0 (0)	0 (0)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1 (0)	1 (0)	6 (2)	6 (2)	1 (0)	2 (1)	2 (1)	3 (1)	2 (1)	2 (1)	2 (1)	0 (0)
7 (2)	5 (2)	4 (1)	2 (1)	1 (0)	0 (0)	3 (1)	2 (1)	1 (0)	0 (0)	0 (0)	0 (0)
2 (1)	4 (1)	1 (0)	0 (0)	0 (0)	0 (0)	3 (1)	2 (1)	1 (0)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
7 (2)	6 (2)	2 (1)	0 (0)	1 (0)	0 (0)	1 (0)	2 (1)	2 (1)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)
54 (17)	27 (8)	24 (7)	6 (2)	0 (0)	0 (0)	26 (9)	20 (7)	4 (1)	5 (2)	0 (0)	2 (1)
24 (7)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)	0 (0)	1 (0)	0 (0)	0 (0)
20 (6)	1 (0)	6 (2)	1 (0)	0 (0)	0 (0)	4 (1)	4 (1)	0 (0)	1 (0)	0 (0)	0 (0)
43 (13)	26 (8)	17 (5)	5 (2)	0 (0)	0 (0)	24 (8)	21 (7)	4 (1)	3 (1)	0 (0)	2 (1)
4 (1)	0 (0)	6 (2)	0 (0)	0 (0)	0 (0)	3 (1)	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)
5 (2)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Tabel S3. Toxicity reported by physicians using the CTCAE v3.0 during treatment and follow-up. (*continued*)

	Maximum grade per patient during treatment CTRT n=327; RT n=326					
	Grade 2		Grade 3		Grade 4	
	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)
Infection/ febrile neutropenia						
Febrile neutropenia	na	na	7 (2)	1 (0)	2 (1)	0 (0)
Infection with neutropenia	3 (1)	0 (0)	6 (2)	0 (0)	1 (0)	0 (0)
Infection without neutropenia	21 (6)	1 (0)	10 (3)	0 (0)	2 (1)	0 (0)
Other	11 (3)	3 (1)	2 (1)	0 (0)	0 (0)	0 (0)
Lymphatics						
Lymphatics	7 (2)	4 (1)	2 (1)	0 (0)	0 (0)	0 (0)
Metabolic / laboratory						
Other	14 (4)	1 (0)	7 (2)	1 (0)	3 (1)	0 (0)
Neurology						
Neuropathy - any	78 (24)	1 (0)	21 (6)	0 (0)	2 (1)	0 (0)
Neuropathy - motor	13 (4)	1 (0)	3 (1)	0 (0)	1 (0)	0 (0)
Neuropathy - sensory	75 (23)	0 (0)	20 (6)	0 (0)	2 (1)	0 (0)
Neurology - other	9 (3)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Pain						
Any	101 (31)	23 (7)	31 (9)	4 (1)	0 (0)	0 (0)
Arthralgia	52 (16)	2 (1)	10 (3)	0 (0)	0 (0)	0 (0)
Myalgia	52 (16)	1 (0)	9 (3)	0 (0)	0 (0)	0 (0)
Pelvic/back/bone/extremity/limbs	10 (3)	4 (1)	11 (3)	0 (0)	0 (0)	0 (0)
Head/headache	6 (2)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Neuralgia	2 (1)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Abdomen NOS	14 (4)	9 (3)	4 (1)	4 (1)	0 (0)	0 (0)
Dyspareunia	6 (2)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Dysuria	25 (8)	7 (2)	1 (0)	0 (0)	0 (0)	0 (0)
Other	14 (4)	0 (0)	4 (1)	0 (0)	0 (0)	0 (0)
Pulmonary						
Dyspnae	12 (4)	2 (1)	5 (2)	0 (0)	0 (0)	0 (0)
Other	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal						
Osteonecrosis	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Other	2 (1)	2 (1)	2 (1)	0 (0)	0 (0)	0 (0)
Renal/genitourinary						
Creatinine	7 (2)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Renal failure	na	na	2 (1)	0 (0)	0 (0)	0 (0)
Incontinence	11 (3)	5 (2)	1 (0)	0 (0)	0 (0)	0 (0)
Fistula	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Obstruction	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urinary frequency/ urgency	22 (7)	10 (3)	2 (1)	2 (1)	na	na
Other	4 (1)	3 (1)	1 (0)	1 (0)	0 (0)	0 (0)
Vascular						
Thrombosis/thrombus/embolism	2 (1)	0 (0)	0 (0)	0 (0)	4 (1)	0 (0)

Abbreviations: CTRT, combined chemotherapy and radiotherapy; RT, radiotherapy; GI, gastro-intestinal; GU, genito-urinary; CTCAE v3.0, Common Terminology Criteria for Adverse Events version 3.0; NA, not applicable. Only grade ≥2 toxicities had to be reported by physicians. All grade 3 and 4 toxicities are reported, and grade 2 toxicities if occurring in ≥10% of patients per time point. There were no grade 5 toxicities. Percentages were rounded to full numbers. AE were calculated at each time point. Per AE, the maximum grade per patient was calculated (worst ever by patient).

Maximum grade per patient at 6 months CTRT n=327; RT n=324						Maximum grade per patient at12 months CTRT n=305; RT n=304					
Grade 2		Grade 3		Grade 4		Grade 2		Grade 3		Grade 4	
CTRT n (%)	RT n (%)	CTRT (n (%)	RT n (%)	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)	CTRT n (%)	RT n (%)
na	na	0 (0)	0 (0)	0 (0)	0 (0)	na	na	0 (0)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5 (2)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	3 (1)	1 (0)	0 (0)	0 (0)	0 (0)
2 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)
5 (2)	6 (2)	1 (0)	0 (0)	0 (0)	0 (0)	8 (3)	3 (1)	2 (1)	1 (0)	0 (0)	0 (0)
2 (1)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	2 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
42 (13)	1 (0)	6 (2)	2 (1)	2 (1)	0 (0)	26 (9)	2 (1)	4 (1)	1 (0)	0 (0)	0 (0)
7 (2)	1 (0)	2 (1)	2 (1)	1 (0)	0 (0)	1 (0)	0 (0)	3 (1)	1 (0)	0 (0)	0 (0)
42 (13	0 (0)	4 (1)	0 (0)	2 (1)	0 (0)	26 (9)	2 (1)	4 (1)	1 (0)	0 (0)	0 (0)
2 (1)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
31 (9)	30 (9)	3 (1)	6 (2)	0 (0)	1 (0)	27 (9)	21 (7)	7 (2)	4 (1)	0 (0)	0 (0)
8 (2)	6 (2)	0 (0)	1 (0)	0 (0)	0 (0)	4 (1)	3 (1)	0 (0)	1 (0)	0 (0)	0 (0)
5 (2)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
10 (3)	8 (2)	0 (0)	3 (1)	0 (0)	0 (0)	12 (4)	5 (2)	3 (1)	1 (0)	0 (0)	0 (0)
2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3 (1)	11 (3)	1 (0)	3 (1)	0 (0)	1 (0)	2 (1)	4 (1)	3 (1)	2 (1)	0 (0)	0 (0)
1 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	5 (2)	4 (1)	1 (0)	0 (0)	0 (0)	0 (0)
4 (1)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)
1 (0)	3 (1)	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	3 (1)	1 (0)	0 (0)	0 (0)	0 (0)
1 (0)	0 (0)	1 (0)	1 (0)	0 (0)	0 (0)	2 (1)	2 (1)	0 (0)	1 (0)	0 (0)	0 (0)
1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3 (1)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
na	na	0 (0)	0 (0)	0 (0)	0 (0)	na	na	0 (0)	0 (0)	0 (0)	0 (0)
6 (2)	7 (2)	1 (0)	0 (0)	0 (0)	0 (0)	8 (3)	9 (3)	1 (0)	1 (0)	0 (0)	0 (0)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)
5 (2)	6 (2)	0 (0)	0 (0)	na	na	4 (1)	8 (3)	0 (0)	1 (0)	na	na
1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3 (1)	0 (0)	0 (0)	0 (0)	2 (1)	1 (0)	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)

Table S4. Complete overview of percentages of patients reporting ´quite a bit´ or ´very much´ HRQL symptoms using the EORTC QLQ-C30, CX-24 and subscales of the OV-28.

		Questionnaire time points						p-value		
				Months						
		Baseline	After RT	6	12	18	24	Changes over time	Difference between groups	Differences between groups over time
QLQ-C30 symptoms										
Dyspnoea	CTRT	5.6	9.8	15.5	6.4	11.2	8.5	**0.001**	**0.01**	0.25
	RT	2.8	5.2	5.1	5.9	3.6	4.5			
Insomnia	CTRT	24.5	24.7	24.2	17.0	19.3	18.0	0.12	0.59	0.96
	RT	19.5	19.0	19.1	13.9	17.1	12.5			
Appetite loss	CTRT	6.6	23.9	10.7	2.6	1.9	2.1	**<0.001**	**0.01**	0.02
	RT	4.5	16.4	4.7	5.4	4.1	4.0			
Constipation	CTRT	10.8	4.7	8.0	3.8	6.3	4.7	**0.009**	0.03	0.10
	RT	7.0	1.3	1.9	4.9	2.6	3.4			
Diarrhoea	CTRT	5.6	36.2	13.2	9.8	9.2	10.0	**<0.001**	0.96	0.92
	RT	3.8	35.9	12.6	11.2	8.4	11.5			
Financial difficulties	CTRT	12.2	10.7	16.0	8.5	7.3	6.3	**<0.001**	0.07	0.30
	RT	7.7	7.5	7.0	3.0	4.7	4.6			
CX-24										
Bowel symptoms										
1. Abdominal cramps	CTRT	6.3	17.2	9.8	9.4	6.8	10.1	**<0.001**	0.85	0.82
	RT	5.0	15.5	8.5	11.3	7.9	7.5			
1. Difficulty controlling bowels	CTRT	2.8	20.5	9.4	8.9	9.2	7.4	**<0.001**	0.48	0.37
	RT	1.4	20.7	11.8	10.0	7.9	12.2			
1. Blood in the stool	CTRT	0.7	1.3	0.9	0.0	0.5	1.6	0.89	0.90	0.90
	RT	0.4	0.4	1.4	0.5	0.0	0.6			
Urinary symptoms										
1. Urinary frequency	CTRT	23.2	37.8	21.0	21.0	19.9	18.6	**<0.001**	0.63	0.51
	RT	22.0	37.5	17.4	24.5	17.1	23.1			
1. Dysuria	CTRT	5.2	16.7	1.4	2.6	3.9	2.1	**<0.001**	0.59	0.46
	RT	4.2	14.2	3.8	3.4	3.7	1.7			
1. Urinary leakage	CTRT	2.8	6.4	7.9	6.8	14.1	9.5	**<0.001**	0.06	0.05
	RT	4.2	4.3	4.7	9.3	7.3	10.9			
1. Difficulty emptying the bladder	CTRT	4.2	4.7	1.9	1.7	3.4	2.1	0.15	0.70	0.58
	RT	2.8	4.8	2.8	3.5	3.1	3.4			
Other										
Swollen legs	CTRT	2.4	4.7	17.8	15.8	17.0	13.3	**<0.001**	0.20	0.45
	RT	2.5	3.0	11.7	11.3	11.1	15.5			

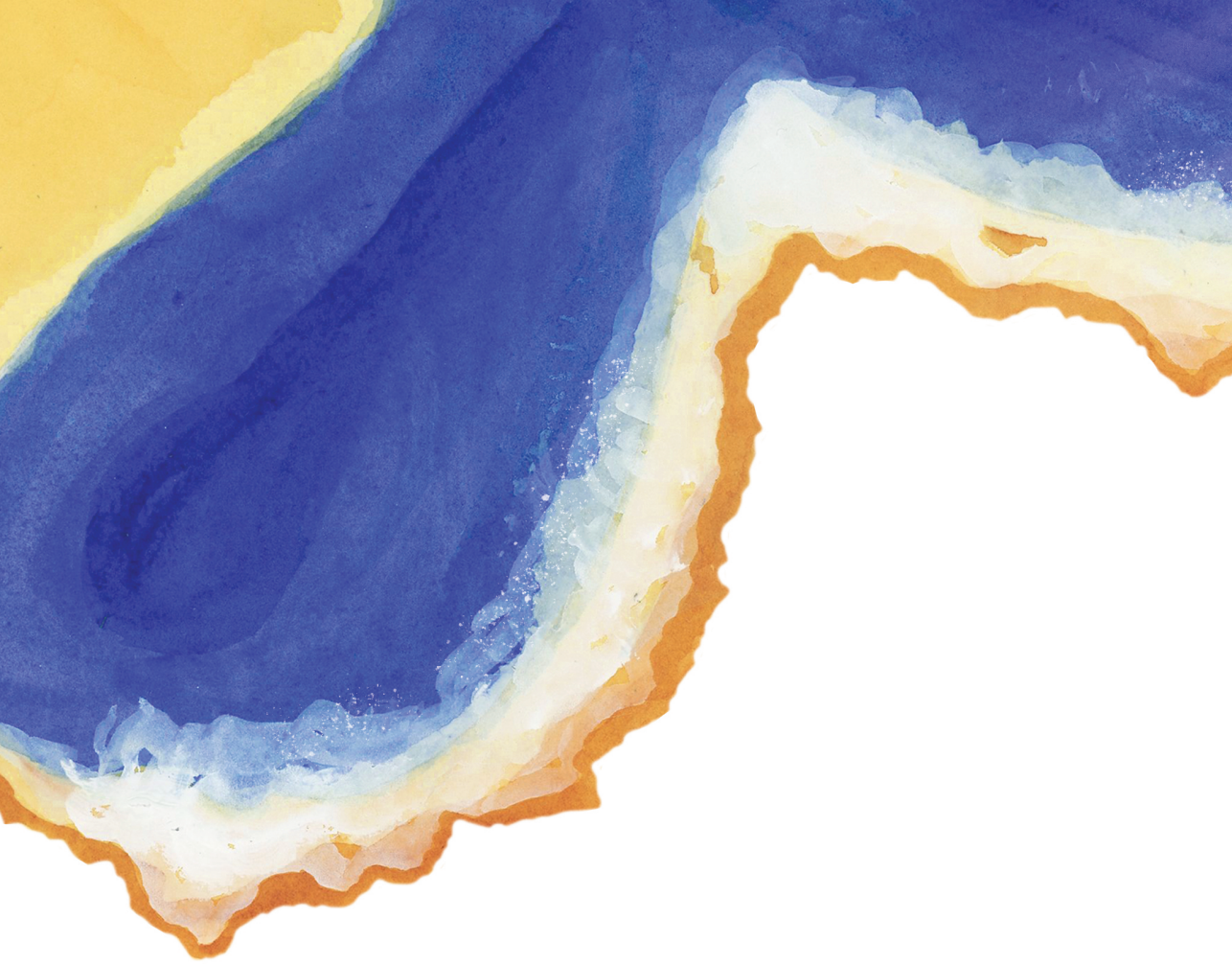
Table S4. Complete overview of percentages of patients reporting ´quite a bit´ or ´very much´ HRQL symptoms using the EORTC QLQ-C30, CX-24 and subscales of the OV-28. (continued)

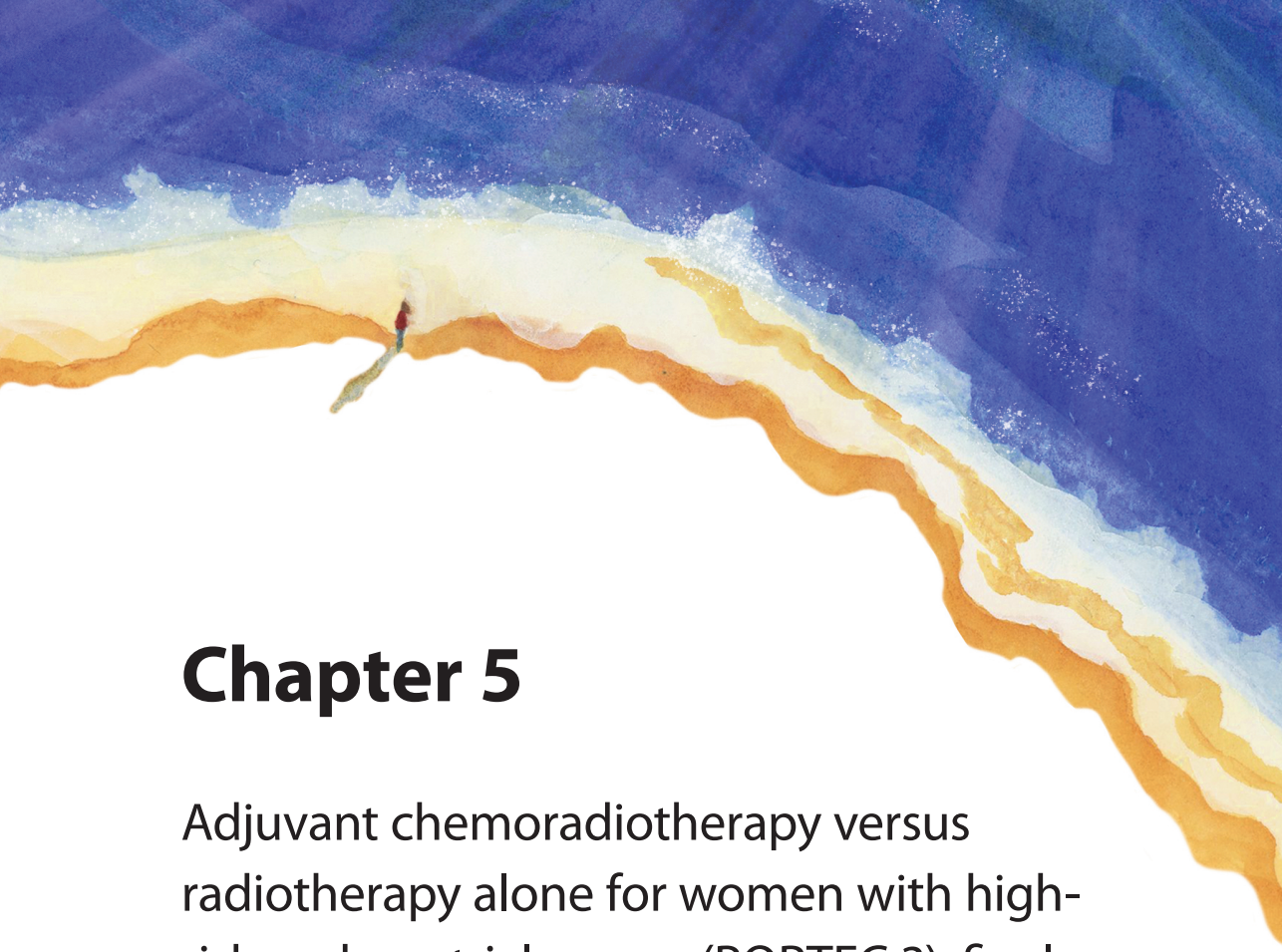
		Questionnaire time points						p-value		
				Months						
		Baseline	After RT	6	12	18	24	Changes over time	Difference between groups	Differences between groups over time
1. Lower back pain	CTRT	10.8	10.3	15.8	18.4	20.2	18.9	**<0.001**	0.93	0.89
	RT	8.8	7.8	16.5	15.1	16.9	17.7			
Tingling/ numbness	CTRT	1.7	6.1	51.9	33.6	24.2	25.3	**<0.001**	**<0.001**	**<0.001**
	RT	1.4	2.6	7.2	10.4	6.3	6.3			
1. Irritation/ soreness vagina/ vulva	CTRT	2.8	8.2	4.7	3.4	1.5	1.6	**0.002**	0.23	0.22
	RT	1.4	11.3	3.8	5.9	4.7	3.4			
1. Vaginal discharge	CTRT	2.8	2.2	2.3	2.1	1.9	0.5	0.78	0.52	0.44
	RT	1.4	4.3	1.4	1.5	0.5	0.6			
1. Vaginal bleeding (abnormal)	CTRT	0.7	0.9	1.9	1.3	0.5	0.0	0.78	0.93	0.93
	RT	1.0	0.4	0.9	0.5	0.5	0.0			
Hot flushes and/or sweats	CTRT	16.3	14.1	19.2	17.9	16.6	15.2	0.35	0.18	0.12
	RT	12.6	15.6	23.9	23.0	17.9	21.4			
2. Feeling of physically less attractive	CTRT	0.5	13.3	24.8	10.2	8.3	8.4	**<0.001**	**<0.001**	0.21
	RT	0.3	6.9	7.5	5.9	5.3	5.2			
2. Feeling of less feminine	CTRT	4.9	8.2	16.7	10.2	7.8	8.9	**<0.001**	0.04	0.38
	RT	3.5	7.0	6.6	6.8	4.7	5.7			
2. Dissatisfied with body	CTRT	5.6	9.0	17.5	13.1	12.7	12.6	**<0.001**	0.27	0.50
	RT	3.9	8.8	9.4	10.3	8.4	7.6			
Sexual functioning										
Worries about sex	CTRT	13.0	20.1	17.6	15.8	15.0	12.5	0.06	0.89	0.81
	RT	14.3	19.2	15.3	14.1	11.4	16.0			
Sexual activity[#]	CTRT	98.1	99.1	96.7	93.8	90.3	94.0	**<0.001**	**0.01**	**0.006**
	RT	98.1	95.4	89.3	90.2	93.6	93.2			
3. Vaginal dryness*	CTRT	10.0	19.6	20.6	27.4	18.8	23.2	0.24	0.36	0.27
	RT	2.1	25.5	21.1	23.3	28.0	32.2			
3. Shortness of vagina*	CTRT	4.2	8.9	7.9	15.3	14.3	24.1	0.12	0.92	0.85
	RT	2.1	10.9	14.1	19.1	16.0	22.8			
3. Tightness of vagina*	CTRT	6.4	28.3	18.2	16.7	18.8	16.4	0.06	0.12	0.07
	RT	4.2	14.8	21.3	21.3	17.3	27.1			
3. Pain during sexual intercourse*	CTRT	0.0	23.8	12.9	9.9	8.7	12.5	0.25	0.35	0.36
	RT	2.3	20.0	17.0	21.1	18.7	26.7			
Sexual activity enjoyable?*	CTRT	63.0	81.6	62.9	60.3	69.1	60.0	0.03	**0.01**	**0.01**
	RT	69.0	54.5	57.6	52.2	52.1	62.7			

Table S4. Complete overview of percentages of patients reporting ´quite a bit´ or ´very much´ HRQL symptoms using the EORTC QLQ-C30, CX-24 and subscales of the OV-28. (continued)

		Questionnaire time points						p-value		
				Months						
		Baseline	After RT	6	12	18	24	Changes over time	Difference between groups	Differences between groups over time
OV 28										
Bloated feeling abdomen/stomach	CTRT	12.6	15.3	18.4	9.4	9.7	11.1	0.03	0.18	0.13
	RT	11.2	14.8	14.4	16.2	13.6	11.6			
Passing wind/ gas/ flatulence	CTRT	16.7	21.0	23.0	19.7	21.2	23.7	0.34	0.33	0.34
	RT	11.4	18.7	21.1	22.1	22.0	18.2			
4. Loss of any hair	CTRT	1.4	10.8	44.0	4.8	4.5	0.5	**<0.001**	**<0.001**	**<0.001**
	RT	0.4	3.5	3.8	3.9	3.1	2.3			
4. Upset by loss of hair**	CTRT	3.3	25.3	41.2	30.0	26.5	12.9	0.05	0.10	0.24
	RT	5.0	3.7	14.3	13.0	7.5	8.3			
4. Different taste of food and drink	CTRT	3.6	27.0	21.7	4.0	4.5	2.2	**<0.001**	**<0.001**	0.03
	RT	0.7	9.8	4.8	3.1	2.7	2.3			
5. Tingling hand/ feet	CTRT	1.1	6.9	49.1	25.8	22.2	23.7	**<0.001**	**<0.001**	**<0.001**
	RT	1.8	2.2	6.3	5.6	4.8	5.3			
5. Numbness fingers/ toes	CTRT	1.4	5.2	49.5	27.8	25.1	25.3	**<0.001**	**<0.001**	**<0.001**
	RT	0.4	2.7	5.3	4.1	3.7	4.1			
5. Weakness arms/ legs	CTRT	6.1	13.5	35.5	16.1	17.1	14.3	**<0.001**	**<0.001**	0.16
	RT	2.9	6.7	11.5	7.2	5.9	6.9			
4. Muscle or joint pain	CTRT	9.7	16.3	37.4	24.0	23.8	24.3	**<0.001**	0.05	0.10
	RT	7.0	13.5	21.7	19.3	23.5	19.1			
4. Problems hearing	CTRT	2.5	3.0	10.8	6.5	8.9	7.4	**<0.001**	0.39	0.52
	RT	2.2	1.8	4.9	6.6	4.3	4.6			

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire C30; CTRT, combined chemotherapy and radiotherapy; RT, radiotherapy; CX, cervix; OV, ovarian; HRQL, health-related quality of life; Tx, treatment. P time: changes of quality-of-life scores over time. P Tx: difference in health-related quality of life between the two treatment groups. P time by Tx: the difference in health-related quality of life between the two treatment groups over time. # this percentage reflects patients who indicated to be not or just a little bit sexually active. * responses to these questions were only expected if the respondent indicated to be sexually active. ** responses to this question was only expected if the respondent indicated to have loss of hair. 1. Symptom experience subscale; 2. Body image subscale; 3. Sexual functioning subscale; 4. Chemotherapy subscale; 5. Peripheral neuropathy subscale.





Chapter 5

Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial

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ABSTRACT

Background

Although women with endometrial cancer generally have a favourable prognosis, those with high-risk disease features are at increased risk of recurrence. The PORTEC-3 trial was initiated to investigate the benefit of adjuvant chemotherapy during and after radiotherapy (chemoradiotherapy) versus pelvic radiotherapy alone for women with high-risk endometrial cancer.

Methods

PORTEC-3 was an open-label, international, randomised, phase 3 trial involving 103 centres in six clinical trials collaborating in the Gynaecological Cancer Intergroup. Eligible women had high-risk endometrial cancer with FIGO 2009 stage I, endometrioid-type grade 3 with deep myometrial invasion or lymph-vascular space invasion (or both), endometrioid-type stage II or III, or stage I to III with serous or clear cell histology. Women were randomly assigned (1:1) to receive radiotherapy alone (48.6 Gy in 1.8 Gy fractions given on 5 days per week) or radiotherapy and chemotherapy (consisting of two cycles of cisplatin 50 mg/m^2 given during radiotherapy, followed by four cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2) using a biased-coin minimisation procedure with stratification for participating centre, lymphadenectomy, stage of cancer, and histological type. The co-primary endpoints were overall survival and failure-free survival. We used the Kaplan-Meier method, log-rank test, and Cox regression analysis for final analysis by intention to treat and adjusted for stratification factors. The study was closed on Dec 20, 2013, after achieving complete accrual; follow-up is ongoing. PORTEC-3 is registered with ISRCTN, number ISRCTN14387080, and ClinicalTrials.gov, number NCT00411138.

Results

686 women were enrolled between Nov 23, 2006, and Dec 20, 2013. 660 eligible patients were included in the final analysis, of whom 330 were assigned to chemoradiotherapy and 330 were assigned to radiotherapy. Median follow-up was 60.2 months (IQR 48.1–73.1). 5-year overall survival was 81.8% (95% CI 77.5–86.2) with chemoradiotherapy versus 76.7% (72.1–81.6) with radiotherapy (adjusted hazard ratio [HR] 0.76, 95% CI 0.54–1.06; p=0.11); 5-year failure-free survival was 75.5% (95% CI 70.3–79.9) versus 68.6% (63.1–73.4; HR 0.71, 95% CI 0.53–0.95; p=0.022). Grade 3 or worse adverse events during treatment occurred in 198 (60%) of 330 who received chemoradiotherapy versus 41 (12%) of 330 patients who received radiotherapy (p<0.0001). Neuropathy (grade 2 or worse) persisted significantly more often after chemoradiotherapy than after radiotherapy (20 [8%] women vs one [1%] at 3 years; p<0.0001). Most deaths were due to endometrial cancer; in four patients (two in each group), the cause of death was

uncertain. One death in the radiotherapy group was due to either disease progression or late treatment complications; three deaths (two in the chemoradiotherapy group and one in the radiotherapy group) were due to either intercurrent disease or late treatment-related toxicity.

Interpretation

Adjuvant chemotherapy given during and after radiotherapy for high-risk endometrial cancer did not improve 5-year overall survival, although it did increase failure-free survival. Women with high-risk endometrial cancer should be individually counselled about this combined treatment. Continued follow-up is needed to evaluate long-term survival.

Funding

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INTRODUCTION

The majority of women with endometrial cancer present with early-stage disease and have a favourable prognosis. About 15% of women with endometrial cancer are diagnosed with high-risk disease, which comprises endometrioid endometrial cancer stage I, grade 3 with deep invasion or with lymph-vascular space invasion (LVSI), stage II or III endometrioid endometrial cancer, or non-endometrioid (serous or clear cell) histology. Women with high-risk endometrial cancer are at increased risk of distant metastases and cancer-related death.[1–4] Serous and clear cell cancers have a higher risk of aggressive spread and a worse prognosis; however, in the early stages they have similar outcomes to grade 3 endometrioid endometrial cancer.[5]

Pelvic external beam radiotherapy has been the standard adjuvant treatment for women with high-risk endometrial cancer for many decades, although there is a paucity of evidence on improvement of survival. Randomised trials[6,7] have compared adjuvant chemotherapy with external beam radiotherapy. Radiotherapy was shown to delay pelvic recurrence and chemotherapy was shown to delay distant metastases, but no differences in survival were found.

Because increased incidence of pelvic relapse has been reported with chemotherapy alone, the combination of external beam radiotherapy with chemotherapy has been explored. In a phase 2 trial (RTOG 9708)[8] among women with high-risk endometrial cancer, the combination of external beam radiotherapy with two concurrent cycles of cisplatin, followed by four adjuvant cycles of cisplatin and paclitaxel, was tested, resulting in 4-year overall survival of 85% and disease-free survival of 81%.

Because the combination of radiotherapy and chemotherapy (chemoradiotherapy) seemed more effective than either treatment alone, and because data for toxicity and quality of life were lacking, the randomised PORTEC-3 trial was initiated to evaluate the benefit of chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer in terms of overall survival and failure-free survival improvement, as well as toxicity and effects on health-related quality of life. Analysis of 2-year toxicity and health-related quality of life in the PORTEC-3 trial showed significantly higher rates of adverse events and reduced health-related quality of life during and after chemoradiotherapy treatment, with rapid recovery thereafter.[9]

Here, we present the final analysis of the primary survival endpoints of the PORTEC-3 trial.

METHODS

Study design and participants

PORTEC-3 was an open-label, randomised, phase 3 trial at 103 centres (oncology centres, university hospitals, regional hospitals, or radiation oncology centres with referrals from regional hospitals) in six clinical trial groups collaborating in the Gynaecological Cancer Intergroup. Participating groups were the National Cancer Research Institute (NCRI; UK), Australia and New Zealand Gynaecologic Oncology Group (ANZGOG; Australia and New Zealand), Mario Negri Gynaecologic Oncology Group (MaNGO; Italy), Canadian Cancer Trials Group (CCTG; Canada), and Fedegyn (France).

Patients were eligible if they had endometrial cancer with either International Federation of Gynecology and Obstetrics (FIGO) 2009 stage 1A endometrioid endometrial cancer grade 3 with documented LVSI; stage IB endometrioid endometrial cancer grade 3; stage II endometrioid endometrial cancer; stage IIIA, IIIB (parametrial invasion), or IIIC endometrioid endometrial cancer; or serous or clear-cell histology endometrial cancer with stages IA (with invasion), IB, II, or III. Eligibility also included WHO performance score 0–2; adequate bone marrow function (white blood cells $\geq 3.0 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L), liver function (bilirubin $\leq 1.5 \times$ upper normal limit [UNL], aspartate aminotransferase and alanine aminotransferase $\leq 2.5 \times$ UNL), kidney function (creatinine clearance >60 mL per min calculated according to Cockroft and Gault[10] or >50 mL per min EDTA clearance), and aged 18 years or older (without an upper age limit, because elderly women might benefit from the study treatment if deemed fit enough to undergo chemotherapy). Exclusion criteria were uterine (carcino)sarcoma; malignancy in the 10 years before diagnosis of endometrial cancer; previous pelvic radiotherapy, hormonal therapy, or chemotherapy; bulky cervical involvement with radical hysterectomy; inflammatory bowel disease; residual macroscopic tumour; impaired renal or cardiac function; grade 2 or worse neuropathy; grade 3 or worse hearing impairment; or congenital hearing disorder.

Surgery comprised total abdominal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy. Lymphadenectomy, whether systemic or sampling, was left to the discretion of participating centres, while lymph node debulking and para-aortic lymph-node sampling were recommended in cases of macroscopic positive pelvic nodes or para-aortic nodes (or both). Lymphadenectomy was not mandated in view of the lack of improvement in overall or progression-free survival in early-stage disease and its associated toxicity, mainly lymph oedema.[11,12] For high-risk disease, the value of lymphadenectomy to direct adjuvant treatment is debated,[13] and the international STATEC trial[14] has been initiated to address this issue. For serous or clear-cell carcinoma, full surgical staging (with omentectomy, peritoneal biopsies, and lymph node sampling) was strongly recommended. Central pathology review by the groups' reference gynae-

copathologists was required before randomisation to confirm patients' final suitability for study entry.

Written informed consent was obtained from all patients. The protocol was approved by the Dutch Cancer Society and by the Ethics Committees of all participating groups. The study protocol is available online.

Randomisation and masking

Patients were randomly allocated (1:1) to chemoradiotherapy or radiotherapy alone. Treatment was allocated with a biased-coin minimisation procedure, ensuring balance overall and within each stratum of the stratification factors (participating centre, lymphadenectomy, stage of cancer, and histological type). Patients were registered and randomised by the participating group's data centres and treatment was assigned via a web-based application. The assigned treatment was generated immediately by the randomisation programme and confirmed by email. Participants and investigators were not masked to treatment allocation.

Procedures

Central pathology review was done by reference gynaecopathologists (as appointed by each participating group before the start of the trial) to determine final eligibility. The slides and blocks were sent to each participating group's central review pathologists at one gynaecological pathology review site (in France and Italy), two sites (in the UK and the Netherlands), or five to six sites (in Australia and New Zealand, and Canada), with the result of the review confirming the patient's eligibility for the trial being sent to the local investigators within 1 week. Details of pathology review and inter-observer variation compared with local pathology assessment are reported separately.[15] In this analysis, review pathology assessment was used. If any particular details were missing, the original pathology was used for these specific items. LVSI was recorded as present or absent. Extensive LVSI in the parametrial tissues was considered stage IIIB. In case of serosal breach, metastases in the stroma of the fallopian tubes, in the ovaries, or on the peritoneal surface of the tubes or ovaries (or both), the stage was defined as IIIA. After determination of eligibility and patient consent, a tumour sample was centrally stored for future translational research.

External beam pelvic radiotherapy was given in both treatment groups to a total dose of 48.6 Gy in 1.8 Gy fractions, 5 days a week. For 11 of the 32 UK sites, a dose of 45 Gy (1.8 Gy fractions) was allowed if specified before initiation of the trial. The clinical target volume included the proximal vagina, parametrial tissues, and internal, external, and common iliac lymph node regions up to the L5–S1 level. The clinical target volume was extended to include the aortic bifurcation in case of iliac lymph node involvement; to include the lower peri-aortic region for common iliac node involvement; and to include

the higher para-aortic region in case of para-aortic involvement (with a margin of ≥2 cm above the highest involved lymph node). If complete bilateral lymphadenectomy had been done with at least 12 lymph nodes, it was recommended to have the upper clinical target volume border at the iliac bifurcation. In case of cervical involvement (glandular, stromal, or both), a brachytherapy boost was given to the vaginal vault. Brachytherapy dose was equivalent to 14 Gy in 2 Gy fractions (with recommended scheme of 10 Gy high-dose rate [HDR] in fractions of 5 Gy), specified at 5 mm from the vaginal vault surface. Most patients were treated with a four-field technique; use of intensity-modulated radiotherapy was allowed for centres per approval by their group's principal investigator. Treatment was recommended to start within 4–6 weeks of surgery, but no later than 8 weeks. Overall radiotherapy treatment time was not to exceed 50 days. Radiotherapy quality assurance was not initially part of the trial, because pelvic radiotherapy was standard practice and used in both groups. However, the Trans-Tasman Radiation Oncology Group (TROG) initiated a bench-marking and quality assurance programme for the ANZGOG group,[16] and in 2012, a protocol amendment allowed a short quality-assurance programme to be activated for all other participating sites, with independent review of a single radiotherapy plan for each site.

Patients in the chemoradiotherapy group received two cycles of intravenous cisplatin 50 mg/m^2 in the first and fourth week of external beam pelvic radiotherapy, followed by four cycles of intravenous carboplatin AUC5 and paclitaxel 175 mg/m^2 at 21-day intervals. This schedule was based on the RTOG-9708 trial,[8] with substitution of cisplatin by carboplatin in the adjuvant phase to reduce toxicity and in view of the use of carboplatin–paclitaxel chemotherapy in metastatic disease.[17]

Adjuvant chemotherapy was to be started within 3 weeks after completion of external beam pelvic radiotherapy, and with a 28-day interval from the second concurrent cycle. Toxicity, however, had to be resolved to better than grade 2 before start of chemotherapy. In the event of toxicities, cisplatin was postponed for 1 week. If recovery required more than 1 week, or in the case of neuropathy of grade 2 or worse, cisplatin was discontinued. Carboplatin was postponed or stopped in case of severe haematological toxicity. Paclitaxel was postponed for grade 2 neuropathy and stopped if recovery exceeded 1 week or grade 3 neuropathy developed. Carboplatin and paclitaxel were delayed for other grade 3–4 toxicities, and discontinued if no recovery or reduction to grade 1 occurred. Details on chemotherapy stopping rules have been described previously.[9]

At each follow-up, patient history was taken with emphasis on toxicities and symptoms of recurrent disease, and physical and pelvic examination were done. Chest radiography, blood count, and chemistry tests (including Ca-125) were to be obtained annually, up to 5 years. Long-term follow-up (by hospital visit or information from the general practitioner) was required at 7 years and 10 years.

Outcomes

The coprimary endpoints were overall survival and failure-free survival. Overall survival was defined as time from date of randomisation to date of death from any cause. Failure-free survival (defined as any relapse or death related to endometrial cancer or treatment) was defined as time from randomisation to date of first failure-free survival event. Failure-free survival events were evaluated by the central data manager, the chief investigator, and the associated investigator, who were unaware of treatment allocation. Women who were alive at the time of analysis were censored at the date of their last follow-up. Secondary endpoints were vaginal, pelvic, or distant recurrence; treatment-related toxicity; and health-related quality of life (published elsewhere[9]). Recurrences were analysed according to first site of recurrence. Abdominal recurrences outside the pelvic area (peritoneal carcinomatosis, liver, and para-aortic lymph nodal metastases) were considered distant metastases, with specification of site.

Toxicity was assessed and graded with Common Terminology Criteria for Adverse Events (CTCAE) version 3.0[18] at baseline (after surgery), at completion of radiotherapy, after each chemotherapy cycle, at 6-month intervals from randomisation until 5 years, and at 7 years and 10 years. Grade 2 or worse adverse events were to be reported, regardless of the association with study treatment. For evaluation of mild (grade 1) toxicities, patient-reported health-related quality-of-life symptoms were used because patient reporting of grade 1 toxicities was considered most reliable.[19] Serious adverse events had to be reported within 24 h, specifying adverse event grade and whether or not they were associated with study treatment.

Statistical analysis

The PORTEC-3 trial was powered (80%) to detect a 10% difference in 5-year overall survival (increase from 65% to 75%; hazard ratio [HR] 0.67), with a two-sided α value of 0.05. 198 events were required, with a minimum number of 655 patients. The number of required patients was increased to 670 to ensure 655 eligible and evaluable patients. Power calculation of the coprimary endpoint failure-free survival was based on the same principles as overall survival.

The first prespecified interim analysis was done after 48 overall survival events (a third of the required events) had occurred in September, 2013, only 3 months before reaching complete accrual. In October, 2016, we decided, with permission from the Data Safety Monitoring Board (DSMB), not to do the prespecified second interim analysis at two-thirds of overall survival events, because this would have no consequences for the trial and would reduce α-spending. To maintain an overall α of 0.05, with a nominal α level for the first interim analysis of 0.0002, the final analysis was done with a nominal α of 0.0498. For analysis of the coprimary endpoints, overall survival and failure-free survival with a correlation between the test-statistics of the coprimary endpoints of 0.7859 (based on

136 overall survival events and 186 failure-free survival events), a nominal α of 0.0309 was used for each of the analyses, resulting in an overall α level of 0.0498.[20]

Because deaths in the PORTEC-3 trial were lower than expected at the time of trial design, the required number of overall survival events was not expected to be reached before late 2018. Recurrence was highest in the first 3 years after treatment, with a sharp decline thereafter, and relapse was rare after 5 years. For these reasons, the DSMB approved the final analysis becoming time-based rather than event-based, with final analysis at a median follow-up of 5 years and 42 months additional follow-up after inclusion of the last patient.

We did statistical analyses using SPSS version 23.0 and R version 3.2.1. All analyses were done by intention to treat, excluding patients who immediately withdrew informed consent and ineligible patients. Differences in relapse and survival rates between the groups were tested with log-rank test and Cox-regression analysis. The analysis of the primary endpoints was adjusted for the stratification factors (participating group, lymphadenectomy, stage of cancer, and histological type), as the appropriate method when using a stratified minimisation procedure at randomisation.[21,22] For adjusted analysis, stratification factors were included as covariates in the Cox model. For analysis of failure-free survival and recurrence, competing-risk methods were used.[23] For failure-free survival, intercurrent death was used as a competing risk. For the first failure analysis of recurrences, all other recurrences and death were used as competing risks. Predictive factors were assessed using Cox regression with treatment-by-covariate interaction including the stratification factors, as well as LVSI and age. The median follow-up was estimated with the reverse Kaplan Meier method.

This study is registered with ISRCTN, number ISRCTN14387080 and ClinicalTrials.gov, number NCT00411138.

Role of the funding source

The funding bodies had no role in study design, data collection, data interpretation, data analysis, or writing of this report. The central data manager (KWV), the chief investigator (CLC), the associated investigators (SMdB, RAN), and the trial statistician (HP) had full access to all the data. The decision to submit for publication was made after discussion within the trial management group and with approval of the DSMB. The corresponding author and chief investigator had full access to all the data and the final responsibility to submit for publication.

RESULTS

Between Nov 23, 2006, and Dec 20, 2013, 686 women were enrolled and randomly assigned to chemoradiotherapy (n=343) or radiotherapy (n=343). 26 patients were excluded: 13 because of immediate informed consent withdrawal and 13 because they did not fulfil the eligibility criteria (figure 1). 660 patients were included in the primary analysis (chemoradiotherapy, n=330; radiotherapy, n=330). Median follow-up was 60.2 months (IQR 48.1–73.1) overall and was 60.0 months (47.8–73.1) in the chemoradiotherapy group and 60.7 months (48.7–72.9) in the radiotherapy group. There were seven major protocol violations: in the chemoradiotherapy group, five patients refused chemotherapy and received radiotherapy only; in the radiotherapy group, two patients asked to switch to chemoradiotherapy (figure 1).

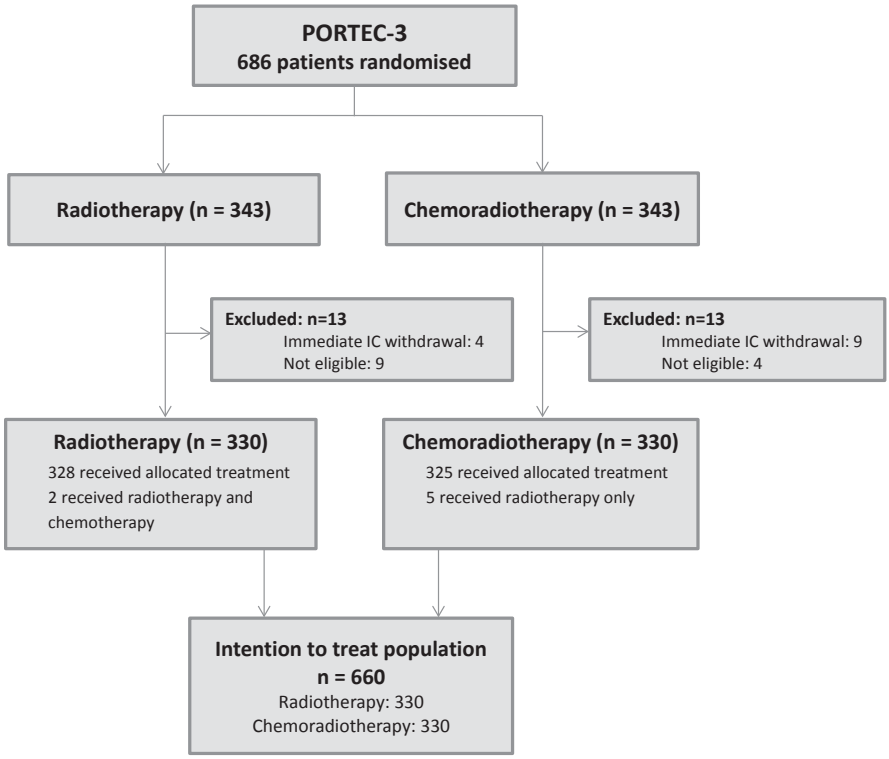


Figure 1. Trial profile

Patient characteristics were well balanced between the treatment groups (table 1). The median age was 62 years (IQR 56.2–68.0). Lymphadenectomy, lymph node sampling, or full surgical staging were done in 190 patients (58%) in the chemoradiotherapy group and in 192 patients (58%) in the radiotherapy group.

Table 1. Patient, tumour and treatment characteristics

	Chemoradiotherapy (n = 330)		Radiotherapy alone (n = 330)	
	No. of patients	%	No. of patients	%
Age at randomisation, years				
Median	62.4		62.0	
Interquartile range	56.5-67.9		55.8-68.2	
< 60 years	128	39%	140	42%
60-69 years	144	44%	128	39%
≥70 years	58	18%	62	19%
Participating groups				
NCRI (United Kingdom)	82	25%	95	29%
DGOG (the Netherlands)	72	22%	66	20%
ANZGOG (Australia and New Zealand)	60	18%	58	18%
MaNGO (Italy)	52	16%	46	14%
CCTG (Canada	36	11%	29	9%
Fedegyn (France)	28	9%	36	11%
FIGO 2009 stage (%)				
Stage IA	39	12%	38	12%
Stage IB	59	18%	59	18%
Stage II	80	24%	90	27%
Stage III	152	46%	143	43%
Histologic grade and type (%)				
EEC grade 1	68	21%	56	17%
EEC grade 2	59	18%	73	22%
EEC grade 3	90	27%	95	29%
Serous	53	16%	52	16%
Clear-cell	29	9%	33	10%
Mixed	17	5%	13	4%
Other	14	4%	8	2%
Myometrial invasion (%)				
<50%	116	35%	123	37%
≥50%	212	65%	206	63%
Missing	2		1	
LVSI (%)				
Yes	197	60%	192	58%
No	133	40%	138	42%
WHO performance (%)				
0 - 1	323	98%	324	98%
≥2	5	2%	5	2%

Table 1. Patient, tumour and treatment characteristics (continued)

	Chemoradiotherapy (n = 330)		Radiotherapy alone (n = 330)	
	No. of patients	%	No. of patients	%
Missing	2		1	
Comorbidity (%)				
Diabetes	45	14%	36	11%
Hypertension	116	35%	104	32%
Cardiovascular	29	9%	20	6%
Type of surgery (%)				
TAH/BSO	95	29%	97	29%
TAH/BSO + LND/full staging	143	43%	131	40%
TLH/BSO	45	14%	41	12%
TLH/BSO + LND/full staging	47	14%	61	18%
Median number of nodes removed (IQR)				
TAH/BSO or TLH/BSO	0	(0-0)	0	(0-0)
TAH/BSO or TLH/BSO +LND/full staging	15	(9-25)	14	(8-22)
Missing	9		16	
Treatment				
Radiation therapy				
EBRT completion	329	100%	325	99%
Dose at prescription point				
Dose <45 Gy	1	<1%	4	1%
Dose 45 Gy - 50.4 Gy	329	100%	322	98%
Dose >50.4 Gy	0	0%	4	1%
Vaginal brachytherapy boost	151	46%	158	48%
Chemotherapy				
Completion				
1 cycle cisplatin	326	99%	-	
2 cycles cisplatin	304	92%	-	
1 cycle Carboplatin/Paclitaxel	302/302	91%/91%	-	
2 cycles Carboplatin/Paclitaxel	294/291	89%/88%	-	
3 cycles Carboplatin/Paclitaxel	279/263	85%/80%	-	
4 cycles Carboplatin/Paclitaxel	262/233	79%/71%	-	

Data are median (IQR) or n (%). NCRI=National Cancer Research Institute. DGOG=Dutch Gynaecological Oncology Group. ANZGOG=Australia and New Zealand Gynaecologic Oncology Group. MaNGO=Mario Negri Gynaecologic Oncology Group. CCTG=Canadian Cancer Trials Group. FIGO=International Federation of Gynecology and Obstetrics. EEC=endometrioid endometrial cancer. LVSI=lymphovascular space invasion. TAH/BSO=total abdominal hysterectomy with bilateral salpingo-oophorectomy. LND=lymph node dissection. TLH=total laparoscopic hysterectomy. EBRT=external beam radiotherapy. *In some cases, both drugs were not given because of toxicities. Missing values are not taken into account for the percentages.

Radiotherapy was discontinued in one patient (<1%) in the chemoradiotherapy group because of disease progression and five patients (1.5%) in the radiotherapy group because of toxicity (table 1). 329 (100%) of 330 patients in the chemoradiotherapy group and 322 (98%) of 330 patients in the radiotherapy group received an external beam pelvic radiotherapy dose between 45.0 and 50.4 Gy. Vaginal brachytherapy was given in 309 (47%) patients (151 [46%] chemoradiotherapy patients vs 158 [48%] radiotherapy patients). Apart from the protocol indication for brachytherapy boost (cervical invasion), 28 (4%) patients received a brachytherapy boost for locally perceived reasons such as LVSI, grade 3, or stage III.

Both cycles of concurrent cisplatin were completed by 304 (92%) of 330 patients in the chemoradiotherapy group. Adjuvant chemotherapy was started by 304 (92%) patients, while 262 (79%) patients completed all four cycles of carboplatin and 233 (71%) patients completed all four cycles of paclitaxel (table 1). At least one dose reduction of cisplatin (to 40 mg/m^2) was recorded for five (2%) patients, of carboplatin (from AUC5 to AUC4) for 36 (11%) patients, and of paclitaxel (from 175 mg/m^2 to 135 mg/m^2) for 50 (15%) patients. Chemotherapy was discontinued in 61 (18%) patients; in 31 (9%) because of toxicity, patient decision in 20 (6%), disease progression in seven (2%), and for other reasons in three (1%).

Evaluation of the TROG quality assurance programme for the ANZGOG group showed that a radiotherapy benchmarking exercise before participation in the trial ensured high conformity and low rates of both minor and major contouring deviations.[16] Evaluation of radiotherapy plans from centres in other countries is ongoing and will be reported separately.

At final database lock on May 1, 2017, 136 patients had died (61 in the chemoradiotherapy group and 75 in the radiotherapy group) and 186 patients had a failure-free survival event (83 in the chemoradiotherapy group and 103 in the radiotherapy group). Among the patients assigned to chemoradiotherapy, 50 (82%) had died from endometrial cancer, four (7%) from a second cancer, three (5%) from other intercurrent disease, and two (3%) from treatment for metastatic disease. Among the patients assigned to radiotherapy, 68 (91%) had died from endometrial cancer and five (7%) from a second cancer. For the remaining four patients (two patients treated with chemoradiotherapy and two patients with radiotherapy), the cause of death was uncertain. In one patient in the radiotherapy group, death was due to either disease progression or late treatment complications; in two patients in the chemoradiotherapy group and one in the radiotherapy group, death was due to either intercurrent disease or late treatment-related toxicity. These four deaths were counted as failure-free survival events after discussion with the DSMB.

Estimated overall survival adjusted for stratification factors at 5 years was 81.8% (95% CI 77.5–86.2) for patients in the chemoradiotherapy group versus 76.7% (72.1–81.6) for

Table 2. Survival and recurrence outcomes

	Events	5-year estimate, % (95% CI)	Hazard ratio (95% CI)	p-value
Overall survival*	-	-	0.76 (0.54 - 1.06)	0.109
Failure free survival*	-	-	0.71 (0.53 - 0.95)	0.022
Overall survival†				
Chemoradiotherapy	61	81.8% (77.5-86.2)	0.81 (0.58 - 1.13)	0.213
Radiotherapy	75	76.7% (72.1–81.6)		
Failure free survival†				
Chemoradiotherapy	83	75.5% (70.3–79.9)	0.76 (0.57 - 1.02)	0.067
Radiotherapy	103	68.6% (63.1–73.4)		
Vaginal recurrence (first recurrence)†				
Chemoradiotherapy	1	0.3% (0.0–2.1)	0.99 (0.06 - 15.90)	0.999
Radiotherapy	1	0.3% (0.0–2.1)		
Pelvic recurrence (first recurrence)†				
Chemoradiotherapy	3	1.0% (0.3–2.9)	0.60 (0.14 - 2.49)	0.473
Radiotherapy	5	1.5% (0.6–3.6)		
Distant metastases (first recurrence)†				
Chemoradiotherapy	76	22.4% (18.1–27.4)	0.78 (0.58 - 1.06)	0.108
Radiotherapy	93	28.3% (23.7–33.7)		
Vaginal recurrence (total)†				
Chemoradiotherapy	8	2.1% (1.0–4.4)	0.99 (0.37 - 2.65)	0.995
Radiotherapy	8	2.1% (1.0–4.4)		
Pelvic recurrence (total)†				
Chemoradiotherapy	16	4.9% (3.0–7.9)	0.51 (0.28 - 0.92)	0.026
Radiotherapy	31	9.2% (6.5–12.9)		
Distant metastases (total)†				
Chemoradiotherapy	79	23.1% (18.8–28.3)	0.77 (0.57 - 1.03)	0.077
Radiotherapy	97	29.7% (24.9–35.1)		

*Data are chemotherapy versus radiotherapy (Cox-adjusted p value), adjusted for stratification factors: participating groups, type of surgery (abdominal hysterectomy and salpingo-oophorectomy vs abdominal surgery plus lymphadenectomy vs laparoscopic procedure vs laparoscopic procedure plus lymphadenectomy), stage (FIGO 2009 IA vs IB vs II vs III), and histological type (endometrioid carcinoma vs serous or clear cell carcinoma). †Log-rank p value, unadjusted for stratification factors.

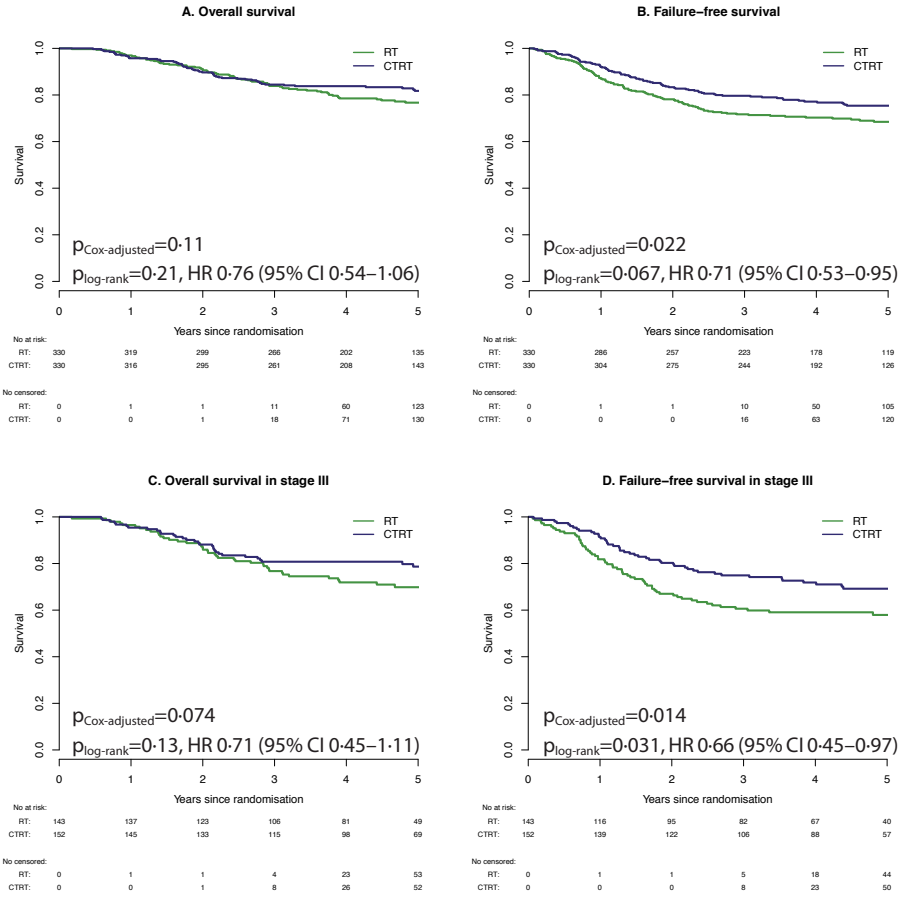


Figure 2. Overall survival and failure-free survival

Kaplan-Meier survival curves for overall survival (A) and failure-free survival (B) in all patients, and for overall survival (C) and failure-free survival (D) of patients with stage III endometrial cancer. $P_{log\text{-}rank}$=unadjusted log-rank p value. $P_{Cox\ adjusted}$=p value adjusted for stratification factors. HR=hazard ratio.

patients in the radiotherapy group (HR 0.76, 95% CI 0.54–1.06; p=0.109; table 2, figure 2). 5-year failure-free survival was 75.5% (70.3–79.9) in the chemoradiotherapy group versus 68.6% (63.1–73.4) in the radiotherapy group (HR 0.71, 0.53–0.95; p=0.022). Without adjusting for the stratification factors, the HR for overall survival was 0.81 (95% CI 0.58–1.13; p=0.213) and for failure-free survival was 0.76 (0.57–1.02; p=0.067; table 2, figure 2).

In subgroup analysis, women with stage III endometrial cancer had significantly lower overall survival and failure-free survival than those with stage I–II disease (tables 3, 4). 5-year overall survival for stage III cancer was 78.7% (95% CI 72.2–85.7) in the chemoradiotherapy group versus 69.8% (62.4–78.1) in the radiotherapy group (HR 0.71, 95% CI

0.45–1.11; p=0.13; adjusted p=0.074). 5-year failure-free survival for stage III cancer was 69.3% (95% CI 61.1–76.2) in the chemoradiotherapy group versus 58.0% (49.3–65.7) in the radiotherapy group (HR 0.66, 95% CI 0.45–0.97; p=0.031; adjusted p=0.014; figure 2). 5-year failure-free survival for stage I–II patients was 80.8% (74.1–86.0) in the chemoradiotherapy group versus 76.6% (69.5–82.2) in the radiotherapy group (0.85, 0.54–1.33; p=0.47).

Serous cancers (>25% serous component) had significantly lower overall survival and failure-free survival than the other histological subtypes; failure-free was 58% (95% CI 42–70) with chemoradiotherapy versus 48% (34–61) with radiotherapy (HR 0.63, 95% CI 0.36–1.12; p=0.11). The number of patients and events are, however, small in these subgroups (appendix Figure S1).

Isolated vaginal and pelvic recurrences were rare, with isolated vaginal recurrence diagnosed in one (<1%) patient in the chemoradiotherapy group and in one (<1%) patient in

Table 3. Multivariable analysis of prognostic factors for overall survival

	Patients (n)	Events (n)	5-year overall survival (95% CI)	Hazard ratio (95% CI)	P value
Total	660	136	79% (74.8–83.9)		
Treatment group					0.075
Radiotherapy (RT)	330	75	77% (72.1–81.6)		
Chemoradiotherapy (CTRT)	330	61	82% (77.5–86.2)	0.73 (0.52-1.03)	
Age (years)					<0.001
< 60 years	268	31	89% (85.0–92.9)		
60-69 years	272	66	75% (69.6–80.6)	2.31 (1.48-3.59)	
≥70 years	120	39	67% (58.7–76.3)	3.29 (1.99-5.44)	
Stage					<0.001
Stage I and II	365	59	83% (79.1–87.3)		
Stage III	295	77	74% (69.3–79.7)	2.41 (1.66-3.51)	
Histology and grade					<0.001
Endometrioid grade 1 and 2	258	36	86% (81.9–90.9)		
Endometrioid grade 3	213	45	79% (73.0–85.7)	1.76 (1.10-2.81)	
Serous / clear cell	189	55	71% (65.2–77.4)	2.35 (1.48-3.72)	
LVSI					0.11
No	271	43	85% (80.5–89.4)		
Yes	389	93	75% (70.9–79.9)	1.36 (0.93-1.98)	
Lymphadenectomy					0.33
No	278	61	77% (71.4–82.1)		
Yes	382	75	81% (77.1–85.2)	0.82 (0.55-1.22)	

Adjusted for participating groups. LVSI = lymph-vascular space invasion.

the radiotherapy group (p=0.995), and isolated pelvic recurrence in three (1%) patients in the chemoradiotherapy group versus five (2%) patients in the radiotherapy group (p=0.473). Most recurrences were distant metastases: 76 (22%) patients in the chemoradiotherapy group versus 93 (28%) patients in the radiotherapy group were diagnosed with distant metastases (p=0.108). The 5-year estimate of pelvic recurrence (both isolated and combined pelvic and distant recurrences) was 4.9% (95% CI 3.0–7.9) for the chemoradiotherapy group versus 9.2% (6.5–12.9) for the radiotherapy group (p=0.026; table 2). In the multivariable analysis, the following covariates were included together with treatment: stage, histological type and grade, type of surgery, participating groups, LVSI, and age. In the presence of these factors, combined chemotherapy and radiotherapy significantly improved failure-free survival. Most factors, except lymphadenectomy, were significantly correlated with failure-free survival (table 4).

Table 4. Multivariable analysis of prognostic factors for failure-free survival

	Patients (n)	Events (n)	5-year failure-free survival (95% CI)	Hazard ratio (95% CI)	P value
Total	660	186	72% (66.7–76.7)		
Treatment group					0.010
Radiotherapy (RT)	330	103	68% (63.1–73.4)		
Chemoradiotherapy (CTRT)	330	83	75% (70.3–79.9)	0.68 (0.51-0.91)	
Age (years)					<0.001
< 60 years	268	54	81% (75.3–85.0)		
60-69 years	272	87	67% (60.7–72.4)	1.74 (1.23-2.46)	
≥70 years	120	45	64% (54.4–71.7)	2.14 (1.41-3.25)	
Stage					<0.001
Stage I and II	365	78	79% (73.9–82.6)		
Stage III	295	108	64% (58.0–69.2)	2.62 (1.90-3.61)	
Histology and grade					<0.001
Endometrioid grade 1 and 2	258	58	78% (72.7–83.1)		
Endometrioid grade 3	213	60	71% (64.5–77.1)	1.56 (1.06-2.30)	
Serous / clear cell	189	68	64% (56.6–70.4)	2.15 (1.46-3.16)	
LVSI					0.054
No	271	62	77% (71.4–81.8)		
Yes	389	124	68% (63.4–72.9)	1.36 (0.99-1.87)	
Lymphadenectomy					0.41
No	278	81	72% (65.7–76.6)		
Yes	382	105	72% (67.4–76.7)	0.87 (0.61-1.22)	

Adjusted for participating groups. LVSI = lymph-vascular space invasion.

In multivariable analysis for failure-free survival, only age group was found to be predictive of treatment effect, with a strong treatment-by-age effect ($p_{interaction}$=0.012, figure 3). Women aged 70 years or older had the greatest benefit from chemoradiotherapy.

Grade 2 or worse adverse events were reported during treatment in 308 (93%) women in the chemoradiotherapy group versus 144 (43%) in the radiotherapy group, and grade 3 or worse in 198 (60%) versus 41 (12%; p<0.0001; table 5); the majority of grade 3 or worse adverse events were haematological. Table 6 shows an overview of adverse events at 6 months after randomisation, which was about 1 month after completion of treatment in the chemoradiotherapy group. There were no treatment-related deaths. From 12 months onwards, no significant differences between the groups were found in grade 3 or worse adverse events (Table S3). The number of patients with grade 2 or worse adverse events was 86 (32%) for chemoradiotherapy versus 64 (24%) for radiotherapy at 3 years (p=0.034), and 57 (40%) versus 38 (28%) at 5 years (p=0.033). The most significant and clinically relevant difference between the arms was found for grade 2 or worse sensory neuropathy, which persisted in 20 (8%) women in the chemoradiotherapy group versus one (1%) women in the radiotherapy group at 3 years and 12 (9%) women versus no women at 5 years (both p<0.0001). An extensive overview of adverse events during follow-up is in the appendix (Table S3).

DISCUSSION

The final results of the PORTEC-3 trial showed that the combination of adjuvant chemotherapy and radiotherapy for high-risk endometrial cancer did not significantly improve overall survival. However, chemoradiotherapy did improve 5-year failure-free survival compared with radiotherapy alone. Patients with stage III disease, who had a higher risk of recurrence than those with stages I–II, had a HR of 0.66 and 11% absolute improvement of failure-free survival with chemo-radiotherapy, which is clinically relevant and exceeds the 10% improvement used when designing the study.

The improvement in failure-free survival in the chemoradiotherapy group should be weighed against the severity and duration of toxicity of combined treatment, especially since overall survival was not significantly improved. Although significantly higher incidences of adverse events and reduced health-related quality of life were reported in the chemoradiotherapy group during and after treatment,[9] rapid recovery was seen, with no differences in grade 3–4 adverse events from 12 months onwards. Grade 2 sensory neuropathy, however, persisted significantly more often in patients treated with chemoradiotherapy, with 25% of patients reporting "quite a bit" or "very much" tingling or numbness at 2 years, compared with 6% for radiotherapy.[9] Sensory neuropathy is associated with lower levels of functioning and quality of life, and more fatigue.[24]

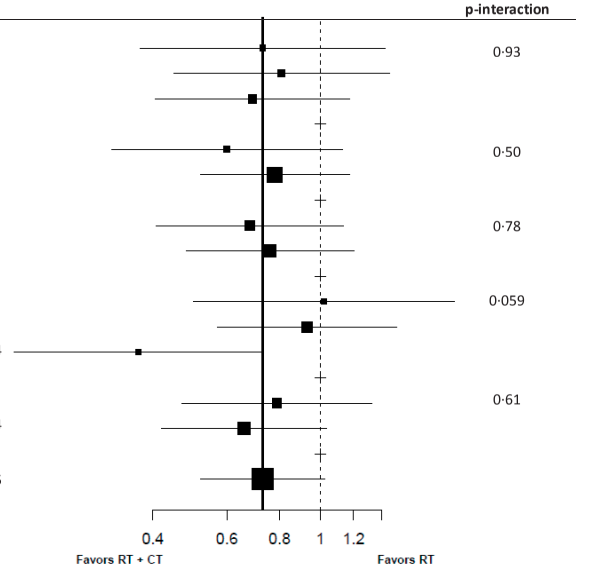
Table 5. Adverse events reported during treatment

	Grade 2			Grade 3-4		
	CTRT n (%)	**RT n (%)**	**P***	**CTRT n (%)**	**RT n (%)**	**p†**
Any	110 (33)	103 (31)	<0.001	198 (60)	41 (12)	<0.001
Any grade 3	na	na		148 (45)	41 (12)	
Any grade 4	na	na		50 (15)	0 (0)	
Auditory or hearing	14 (4)	3 (1)	0.01	1 (0)	1 (0)	1.00
Allergy	23 (7)	1 (0)	<0.001	5 (2)	0 (0)	0.06
Fatigue	69 (21)	7 (2)	<0.001	10 (3)	0 (0)	0.002
Hypertension	19 (6)	12 (4)	0.14	6 (2)	3 (1)	0.50
Alopecia	187 (57)	1 (0)	<0.001	na	na	
Dermatitis	18 (5)	5 (2)	0.01	1 (0)	1 (0)	1.0
Any gastrointestinal	145 (44)	79 (24)	<0.001	47 (14)	18 (5)	<0.001
Diarrhea	104 (32)	69 (21)	<0.001	35 (11)	14 (4)	0.003
Nausea	68 (21)	24 (7)	0.001	9 (3)	2 (1)	0.06
Vomiting	31 (9)	9 (3)	<0.001	5 (2)	0 (0)	0.06
Anorexia	30 (9)	9 (3)	0.003	3 (1)	4 (1)	1.00
Constipation	32 (10)	6 (2)	<0.001	1 (0)	0 (0)	1.00
Genito-urinary – frequency or urgency	24 (7)	10 (3)	0.02	2 (1)	2 (1)	1.00
Any hematological	100 (30)	19 (6)	<0.001	149 (45)	18 (5)	<0.001
Febrile neutropenia	na	na		9 (3)	1 (0)	0.02
Infection with neutropenia	3 (1)	0 (0)	0.002	7 (2)	0 (0)	0.02
Infection without neutropenia	21 (6)	1 (0)	<0.001	12 (4)	1 (0)	<0.001
Hemoglobin	105 (32)	0 (0)	<0.001	27 (8)	0 (0)	<0.001
Leucocytes	98 (30)	3 (1)	<0.001	76 (23)	1 (0)	<0.001
Lymphocytes	48 (15)	16 (5)	<0.001	109 (33)	17 (5)	<0.001
Neutrophils	62 (19)	1 (0)	<0.001	66 (20)	1 (0)	<0.001
Platelets	22 (7)	0 (0)	<0.001	18 (5)	0 (0)	<0.001
Metabolic or laboratory	15 (5)	1 (0)	<0.001	3 (1)	0 (0)	0.25
Any neuropathy	82 (25)	1 (0)	<0.001	23 (7)	0 (0)	<0.001
Motor	13 (4)	1 (0)	<0.001	4 (1)	0 (0)	0.12
Sensory	79 (24)	0 (0)	<0.001	22 (7)	0 (0)	<0.001
Any pain	101 (31)	23 (7)	<0.001	31 (9)	4 (1)	<0.001
Joint	52 (16)	2 (1)	<0.001	10 (3)	0 (0)	0.002
Muscle	52 (16)	1 (0)	<0.001	9 (3)	0 (0)	0.004
Pelvic, back or limb	10 (3)	4 (1)	<0.001	11 (3)	0 (0)	<0.001
Pulmonary - dyspnea	12 (4)	2 (1)	<0.001	5 (2)	0 (0)	0.06
Thrombosis or embolism	2 (1)	0 (0)	0.03	4 (1)	0 (0)	0.12

Data are n (%). Adverse events are listed that occurred in at least 5% of patients, or were significantly different between the study groups at any timepoint during treatment, or both. Adverse events were calculated at each timepoint. For each adverse event, the maximum grade per patient was calculated (worst ever by patient). Adverse events were graded according to Common Terminology Criteria for Adverse Events version 3.0. Chemoradiotherapy, n=330; radiotherapy, n=330. NA=not applicable. *Significance level for grade 2, 3, and 4. †Significance level for grade 3 and 4.

A. Overall survival

	Radiotherapy				Chemoradiotherapy				Chemoradiotherapy vs radiotherapy			
	No. pts	No. of events	5-yr FFS	95% CI	No. pts	No. of events	5-yr FFS	95% CI	HR	95% CI	p	p-interaction
Histology and grade												
Endometrioid grade 1- 2	131	21	84%	78-91	127	15	88%	82-94	0·73	0·37-1·42	0·35	0·93
Endometrioid grade 3	106	23	77%	69-86	107	22	80%	73-89	0·81	0·45-1·47	0·49	
Serous, clear cell, other	93	31	66%	56-76	96	24	76%	68-85	0·69	0·41-1·19	0·19	
LVSI												
No	138	25	82%	76-89	133	18	88%	82-94	0·60	0·32-1·13	0·11	0·50
Yes	192	50	73%	67-80	197	43	77%	71-84	0·78	0·52-1·18	0·25	
Lymphadenectomy												
No	138	33	75%	67-83	140	28	78%	71-86	0·68	0·41-1·14	0·15	0·78
Yes	192	42	78%	72-85	190	33	84%	79-90	0·76	0·48-1·20	0·24	
Age												
<60	140	16	89%	83-94	128	15	89%	84-95	1·02	0·50-2·08	0·96	0·059
60-69	128	33	72%	64-81	144	33	78%	71-85	0·93	0·57-1·52	0·77	
≥70	62	26	58%	47-72	58	13	76%	65-89	0·37	0·19-0·74	0·004	
FIGO stage												
stage I and II	187	32	82%	76-88	178	27	84%	79-90	0·79	0·47-1·33	0·38	0·61
stage III	143	43	70%	62-78	152	34	79%	72-86	0·66	0·42-1·04	0·074	
Total	330	75	77%	72-82	330	61	82%	78-86	0·73	0·52-1·03	0·075	



B. Failure-free survival

	Radiotherapy				Chemoradiotherapy				Chemoradiotherapy vs radiotherapy			
	No. pts	No. of events	5-yr FFS	95% CI	No. pts	No. of events	5-yr FFS	95% CI	HR	95% CI	p	p-interaction
Histology and grade												
Endometrioid grade 1- 2	131	32	75%	66-82	127	26	82%	74-88	0·74	0·44-1·26	0·27	0·79
Endometrioid grade 3	106	32	69%	59-77	107	28	74%	64-81	0·73	0·44-1·22	0·23	
Serous, clear cell, other	93	39	59%	48-68	96	29	69%	58-77	0·60	0·37-0·97	0·036	
LVSI												
No	138	32	77%	68-83	133	30	78%	69-84	0·80	0·48-1·33	0·39	0·45
Yes	192	71	63%	55-69	197	53	74%	67-80	0·63	0·44-0·90	0·012	
Lymphadenectomy												
No	138	46	67%	58-74	140	35	76%	68-83	0·58	0·37-0·91	0·016	0·34
Yes	192	57	70%	63-76	190	48	75%	68-81	0·77	0·52-1·14	0·19	
Age												
<60	140	26	81%	73-87	128	28	81%	72-87	1·17	0·68-2·00	0·57	0·012
60-69	128	47	62%	53-71	144	40	71%	62-79	0·69	0·45-1·06	0·094	
≥70	62	30	53%	40-65	58	15	75%	61-85	0·33	0·18-0·63	<0·001	
FIGO stage												
stage I and II	187	43	77%	70-82	178	35	81%	74-86	0·77	0·49-1·21	0·26	0·47
Stage III	143	60	58%	49-66	152	48	69%	61-76	0·62	0·42-0·91	0·014	
Total	330	103	69%	63-73	330	83	76%	70-80	0·68	0·51-0·91	0·010	

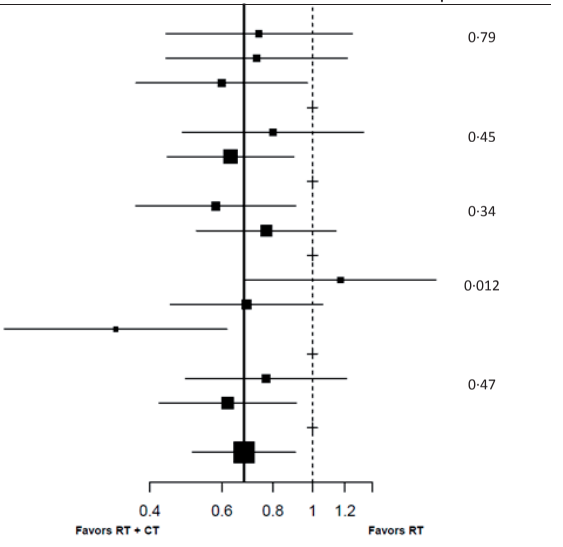


Figure 3. Forest plot of multivariable analysis (treatment by covariate interaction) of overall survival (A) and failure-free survival (B)
For the multivariable analysis the stratification factors (participating group, lymphadenectomy, stage of cancer, and histological type), lymphovascular space invasion, and age were used. HR=hazard ratio. LVSI=lymphovascular space invasion. FIGO=International Federation of Gynecology and Obstetrics.

Table 6. Adverse events reported at 6 months after randomisation

	Grade 2			Grade 3-4		
	CTRT n (%)	RT n (%)	P*	CTRT n (%)	RT n (%)	p†
Any	128 (39)	96 (29)	<0.001	54 (16)	25 (8)	<0.001
Any grade 3	na	na		49 (15)	21 (6)	
Any grade 4	na	na		5 (2)	4 (1)	
Auditory or hearing	8 (2)	3 (1)	0.22	0 (0)	0 (0)	1.00
Allergy	2 (1)	1 (0)	1.00	0 (0)	0 (0)	1.00
Fatigue	10 (3)	2 (1)	0.05	1 (0)	1 (0)	1.00
Hypertension	15 (5)	18 (5)	0.75	5 (2)	5 (2)	1.00
Alopecia	64 (19)	0 (0)	<0.001	na	na	
Dermatitis	1 (0)	0 (0)	1.00	0 (0)	0 (0)	1.00
Any gastrointestinal	19 (6)	18 (5)	0.89	7 (2)	9 (3)	0.80
Diarrhea	8 (2)	11 (3)	0.20	0 (0)	3 (1)	0.25
Nausea	7 (2)	5 (2)	0.35	5 (2)	2 (1)	0.45
Vomiting	7 (2)	6 (2)	0.45	3 (1)	0 (0)	0.25
Anorexia	1 (0)	4 (1)	0.50	2 (1)	2 (1	1.00
Constipation	7 (2)	4 (1)	0.79	1 (0)	2 (1)	1.00
Genito-urinary – frequency or urgency	5 (2)	6 (2)	0.77	1 (0)	0 (0)	1.00
Any hematological	54 (16)	27 (8)	<0.001	24 (7)	6 (2)	0.001
Febrile neutropenia	na	na		0 (0)	0 (0)	1.00
Infection with neutropenia	0 (0)	0 (0)	1.00	1 (0)	0 (0)	1.00
Infection without neutropenia	5 (2)	1 (0)	0.22	0 (0)	0 (0)	1.00
Hemoglobin	24 (7)	0 (0)	<0.001	3 (1)	0 (0)	0.25
Leucocytes	20 (6)	1 (0)	<0.001	6 (2)	1 (0)	0.12
Lymphocytes	43 (13)	26 (8)	0.002	17 (5)	5 (2)	0.02
Neutrophils	4 (1)	0 (0)	0.002	6 (2)	0 (0)	0.03
Platelets	5 (2)	0 (0)	0.02	2 (1)	0 (0)	0.50
Metabolic or laboratory	2 (1)	0 (0)	0.12	2 (1)	0 (0)	0.50
Any neuropathy	42 (13)	1 (0)	<0.001	8 (2)	2 (1)	0.11
Motor	7 (2)	1 (0)	0.09	3 (1)	2 (1)	1.00
Sensory	41 (12)	0 (0)	<0.001	6 (2)	0 (0)	0.03
Any pain	31 (9)	32 (10)	0.54	3 (1)	7 (2)	0.34
Joint	8 (2)	6 (2)	1.00	0 (0)	1 (0)	1.00
Muscle	5 (2)	1 (0)	0.22	0 (0)	0 (0)	1.00
Pelvic, back or limb	10 (3)	9 (3)	0.33	0 (0)	3 (1)	0.25
Pulmonary - dyspnea	1 (0)	0 (0)	1.00	1 (0)	1 (0)	1.00
Thrombosis or embolism	3 (1)	0 (0)	0.37	1 (0)	1 (0)	1.00

Data are n (%). Adverse events are listed that occurred in at least 5% of patients, or were significantly different between the study groups at any timepoint, or both. Adverse events were calculated at each timepoint. For each adverse event, the maximum grade per patient was calculated (worst ever by patient). Adverse events were graded according to Common Terminology Criteria for Adverse Events version 3.0. Chemoradiotherapy, n=329; radiotherapy, n=329. NA=not applicable. *Significance level for grade 2, 3, and 4. †Significance level for grade 3 and 4.

For decades, standard adjuvant treatment for women with high-risk endometrial cancer has been pelvic external beam radiotherapy. It has been hypothesised that chemotherapy might improve survival by reducing the risk of metastatic disease. Randomised trials comparing adjuvant chemotherapy with external beam radiotherapy failed to show an improvement in progression-free survival or overall survival.[6,7] Retrospective studies reported substantial rates of pelvic recurrence if high-risk patients were treated without radiotherapy, supporting the combined use of pelvic radiotherapy with adjuvant chemotherapy, as first explored in the RTOG 9708 phase 2 trial.[8,25,26]

Randomised studies have compared radiotherapy with the combination of chemotherapy and radiotherapy in patients with high-risk endometrial cancer. The NSGO-EC-9501/EORTC-55991 trial compared external beam radiotherapy alone with external beam radiotherapy and four cycles of platinum-based chemotherapy, given sequentially before or after external beam radiotherapy. A pooled analysis with the ManGO Iliade 3 trial[27] with a total cohort of 534 patients showed, in line with our results, improved progression-free survival (78% vs 69%, p=0.01) and a trend for improved survival (82% vs 75%, p=0.07) with the addition of chemotherapy to radiotherapy alone.

The schedule of combined radiotherapy with concurrent and adjuvant chemotherapy used in the PORTEC-3 trial seemed likely to be most effective because both treatments were started early after surgery and thus maximum benefit of the combination could be expected. In RTOG-9708, 4-year overall survival was 85% and disease-free survival was 81%. A retrospective single institution study[28] reporting on 40 patients with stage IIIA or IIIC endometrial cancer treated with the same combination of chemoradiotherapy showed 5-year overall survival of 85% and relapse-free survival of 79%. In the chemoradiotherapy group of the PORTEC-3 trial the 5-year overall survival probability was 82% and the failure-free survival probability was 76%, thus confirming these results in a much larger trial. Overall and relapse-free survival in the pooled NSGO-EC-9501/EORTC-55991/Iliade trials[27] were also similar at 82% and 78%, with only 20% patients with stage III disease.

High-risk endometrial cancer is heterogeneous, including various histological types and stages of disease. In the NSGO-EC-9501/EORTC-55991 trial, although progression-free survival was significantly improved for patients with endometrioid endometrial cancer, this improvement was not found for serous and clear cell cancers. A Gynecologic Oncology Group (GOG) study[29] explored the associations between histology and outcome in advanced or recurrent endometrial cancer patients in chemotherapy trials in 1203 patients. Although serous and clear cell cancers had a worse prognosis than other histological types, no difference in benefit from chemotherapy was found. In the PORTEC-3 trial, women with serous or clear-cell cancers had at least as much improvement in failure-free survival with the addition of chemotherapy as women with endometrioid endometrial cancer did. When comparing serous cancers with other histological types, as

expected, worse overall survival and failure-free survival were found for serous cancers; patients with serous cancers had a failure-free survival benefit with chemoradiotherapy, but this benefit was not significant in view of the small numbers of serous cancers and events.

The multivariable analysis indicated that women older than 70 years seemed to have a greater failure-free survival benefit from chemotherapy than younger women. Age is a well-known risk factor for endometrial cancer and a greater benefit of chemotherapy in older women has been reported previously.[7,30] Although selection of fitter older women in this randomised trial might have occurred, physicians should not be reticent to counsel older women about the possible benefits of combined chemotherapy and radiotherapy. Analysed by stage, patients with stage III endometrial cancer who have the highest frequency of recurrence, also had the greatest absolute benefit from the combined treatment. The smaller failure-free survival improvement for patients with stage I–II disease seems not to outweigh the cost in terms of toxicity and quality-of-life impairment. Pelvic control was high (91%) with radiotherapy alone. This finding is in line with the results of the GOG-249 trial, in which patients with stage I and II endometrial cancer with high-intermediate or high-risk factors were randomly assigned to pelvic radiotherapy alone or to chemotherapy (three cycles of carboplatin and paclitaxel) followed by vaginal brachytherapy. No superiority of three cycles chemotherapy plus vaginal brachytherapy over external bean radiotherapy alone was found, with overlapping progression-free and overall survival curves and significantly more pelvic and para-aortic recurrences in the chemotherapy group.[31,32]

In 47% of all patients, a vaginal brachytherapy boost was given (46% for chemoradiotherapy vs 48% for radiotherapy); the majority because of cervical involvement and 4% because of other reasons, such as LVSI or grade 3 endometrial cancer. This finding is in line with other studies among patients with stage II–III endometrial cancer.[33] Although the addition of a brachytherapy boost might have added to the good local control seen in both groups, we do not expect this would have affected the results, because the proportion of women receiving a brachytherapy boost was equal in the two treatment groups.

To compare the radiotherapy and chemotherapy schedule as used in the PORTEC-3 trial with chemotherapy alone for advanced stage endometrial cancer, the GOG-258 trial randomly assigned participants to receive chemoradiotherapy or six cycles of carboplatin and paclitaxel.[34] Final results are pending, but a presented abstract[34] reported no differences in overall or recurrence-free survival, while significantly more vaginal and pelvic or para-aortic recurrences were reported in patients treated with chemotherapy alone. Similar results were also reported in a retrospective multicentre study[35] of 265 patients with stage IIIC disease treated with chemotherapy, radiotherapy, or both. Patients treated with chemotherapy alone were two to seven times more likely to develop a vagi-

nal recurrence (35%) than those treated with radiotherapy (18%) or chemoradiotherapy (5%), and twice as likely to develop an isolated pelvic recurrence (18% vs 9% vs 7%). These outcomes confirm the importance of combined radiotherapy and chemotherapy to maximise vaginal and pelvic control and relapse-free survival. Furthermore, acute gastrointestinal and genitourinary toxicity of pelvic radiotherapy will be reduced with the current standard use of intensity-modulated radiotherapy.[36]

PORTEC-3 was a multicentre trial with strong international collaboration among six participating groups and, therefore, highly representative of current practice worldwide. Upfront pathology review was done to include only truly high-risk patients in the trial. Analysis of pathology review in the Netherlands and the UK (48% of PORTEC-3 participants) revealed that 8.3% of patients did not fulfil the eligibility criteria after central pathology review. These patients did not enter the trial.[15]

A limitation of this trial might be that because of the death and failure-free survival event rates were lower than expected at the time of trial design, the required number of overall survival events was not reached and the final analysis was time-based rather than event-based, with final analysis at a median follow-up of 5 years (42 months after inclusion of the last patient). The number of overall survival events was 136 (69% of the required number of overall survival events), and the number of failure-free survival events was 186 (94% of the required events). The non-significant difference in 5-year overall survival of 5% found in PORTEC-3 was smaller than the study was powered to detect, and overall survival and failure-free survival probabilities were higher than expected from previous studies. Long-term outcomes will be analysed, especially for overall survival.

The costs of chemoradiotherapy in terms of toxicity and treatment duration should be weighed against the benefits, and this cost–benefit trade-off could be seen differently from the patient or physician perspective. In a patient preference study done by the ANZGOG group among PORTEC-3 participants,[37] more than 50% of patients rated 5% survival improvement sufficient to make chemotherapy worthwhile. Although the trial results are in the range of this benefit for failure-free survival, the overall survival difference was not significant, thus individual patient counselling remains essential. Translational studies of molecular risk factors and tumour characteristics with the tumour samples of the PORTEC-3 participants might identify those who could most benefit from chemotherapy or targeted agents and individualise treatment of women with high-risk endometrial cancer.[38]

In conclusion, although treatment with chemoradiotherapy significantly improved 5-year failure-free survival for patients with high-risk endometrial cancer compared with radiotherapy alone, there was no significant difference in overall survival. For women with stage III endometrial cancer, a significant improvement in failure-free survival was found. For each patient, the cost in terms of increased toxicity and longer treatment

duration should be weighed against the benefit in terms of improvement in failure-free survival. Because pelvic control was high with radiotherapy alone, this chemoradiotherapy schedule cannot be recommended as a new standard for patients with stage I–II endometrial cancer. However, in view of the higher risk of recurrence among women with stage III disease, this chemoradiotherapy schedule should be considered to maximise failure-free survival, and benefits and risks should be individually discussed.

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SUPPLEMENTARY MATERIAL

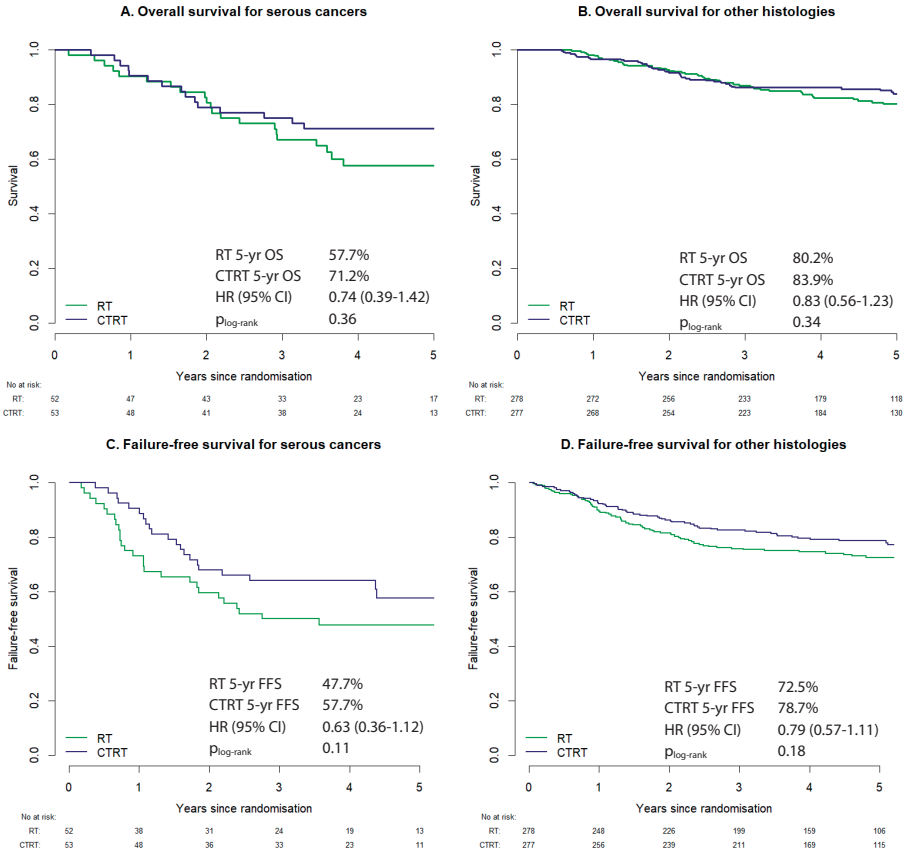


Figure S1. Kaplan-Meier survival curve for overall survival for serous cancers (A) and other histologies (B) and failure free survival curve for serous cancers (C) and other histologies (D).

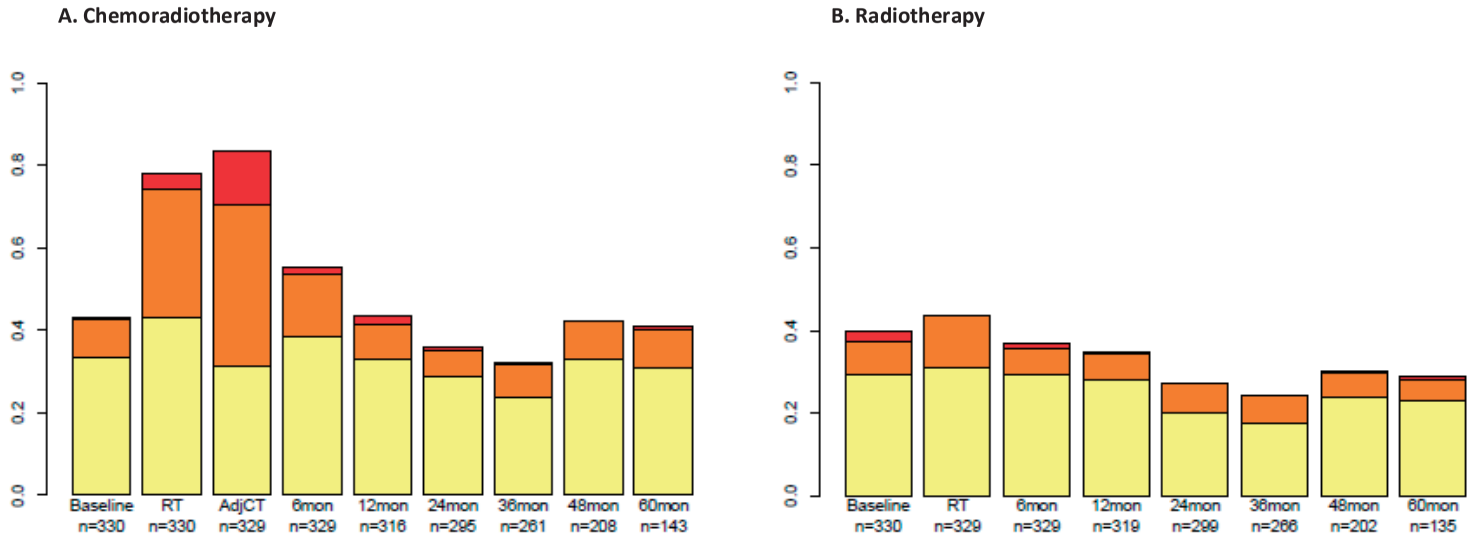


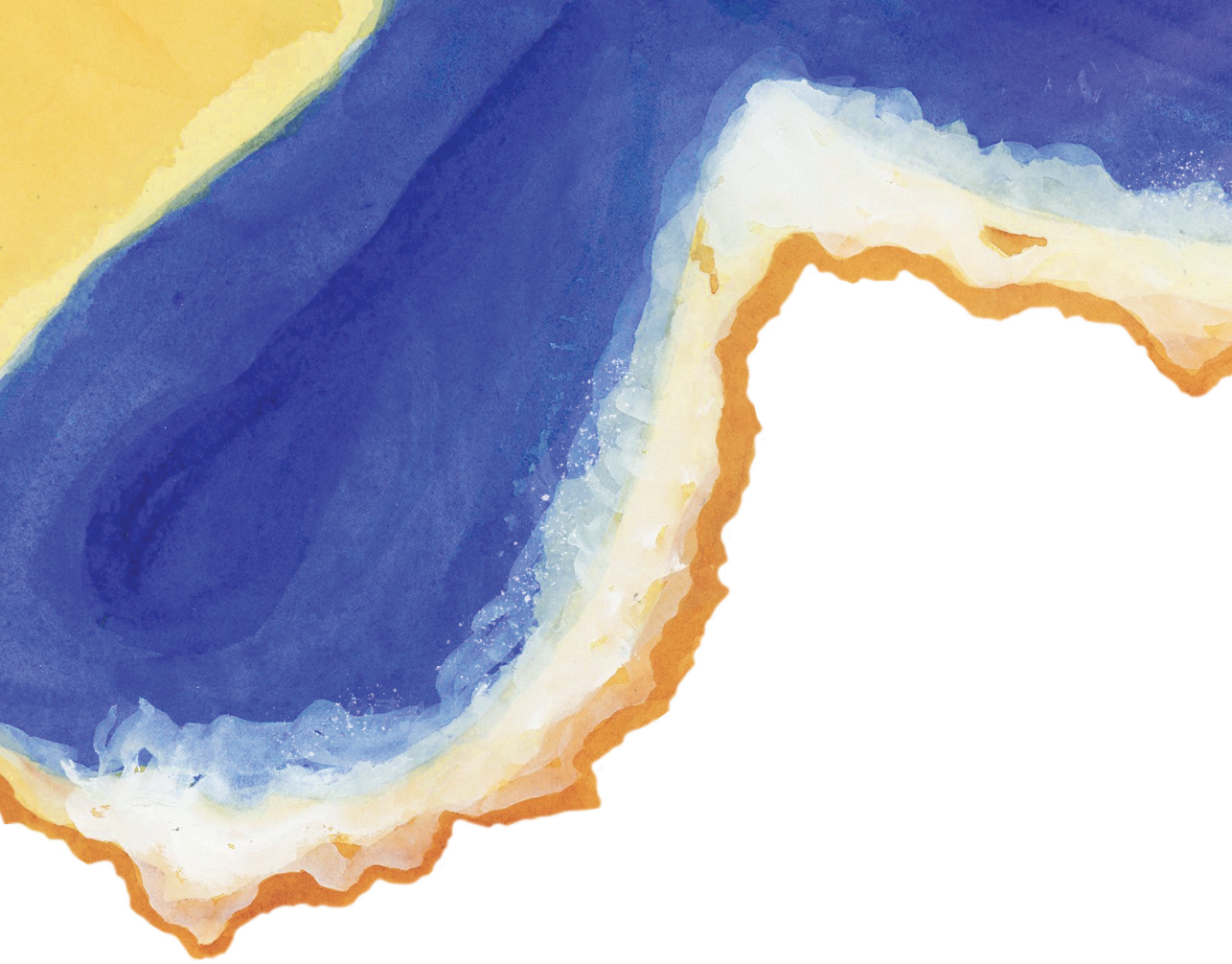
Figure S2. Incidence of the maximum physician-reported adverse events grades per patient for each timepoint at baseline, during treatment and at 6, 12, 24, 36, 48 and 60 months follow-up in the chemoradiotherapy group (A) and the radiotherapy alone group (B)

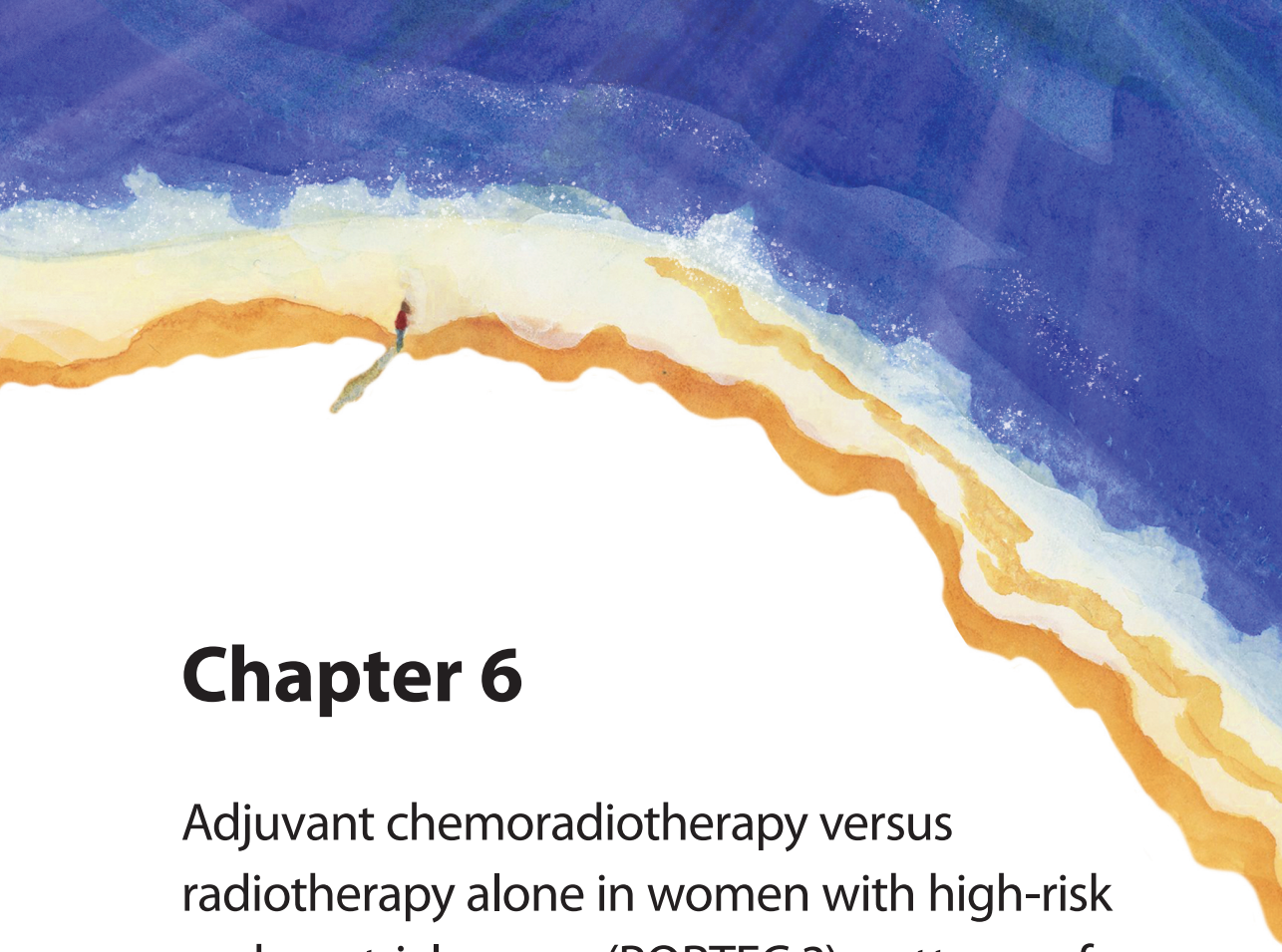
Table S3. Adverse events reported during follow-up at 12, 36 and 60 months after randomisation.

	Adverse events at 12 months after randomisation CTRT n=317; RT n=316					
	Grade 2			Grade 3-4		
	CTRT n (%)	RT n (%)	P*	CTRT n (%)	RT n (%)	p#
Any	103 (33)	89 (28)	0·04	33 (10)	21 (7)	0·09
Any grade 3	na	na		27 (9)	19 (6)	
Any grade 4	na	na		6 (2)	2 (1)	
Auditory or hearing	10 (3)	2 (1)	0·02	0 (0)	0 (0)	1·00
Fatigue	5 (2)	4 (1)	1·00	0 (0)	2 (1)	0·50
Hypertension	14 (4)	17 (5)	0·62	4 (1)	5 (2)	1·00
Lymphatics (edema)	8 (3)	3 (1)	0·11	2 (1)	1 (0)	0·62
Any gastrointestinal	21 (7)	19 (6)	0·24	7 (2)	2 (1)	0·11
Diarrhea	11 (3)	8 (3)	0.39	1 (0)	1 (0)	1·00
Ileus or obstruction	2 (1)	3 (1)	0.77	4 (1)	2 (1)	0·45
Any hematological	26 (8)	21 (7)	0·89	4 (1)	7 (2)	0·54
Lymphocytes	24 (8)	22 (7)	0·89	4 (1)	5 (2)	1·00
Any neuropathy	26 (8)	1 (0)	<0·001	4 (1)	1 (0)	0·22
Motor	1 (0)	0 (0)	0·22	3 (1)	1 (0)	0·37
Sensory	26 (8)	1 (0)	<0·001	4 (1)	1 (0)	0·22
Any pain	26 (8)	22 (7)	0·18	8 (3)	3 (1)	0·14
Joint	4 (1)	3 (1)	0·72	0 (0)	0 (0)	1·00
Muscle	4 (1)	1 (0)	0.22	0 (0)	0 (0)	1·00
Back, pelvic or limbs	11 (3)	5 (2)	0·05	3 (1)	1 (0)	0·37
Abdomen or cramps	2 (1)	5 (2)	0.77	3 (1)	2 (1)	0·69
Pulmonary - Dyspnea	2 (1)	2 (1)	1.00	0 (0)	1 (0)	1·00
GU - incontinence	8 (3)	9 (3)	1·00	1 (0)	1 (0)	1·00
GU – obstruction	0 (0)	0 (0)	1.00	0 (0)	1 (0)	1·00
GU - urinary frequency	4 (1)	8 (3)	0·26	0 (0)	1 (0)	1·00

All adverse events are listed which were grade >3, or occurred in >5% of patients, or were significantly different between the study arms. Abbreviations: CTRT, combined chemotherapy and radiotherapy; RT, radiotherapy; GU, genito-urinary; na, not applicable. AE were calculated at each time point. Per AE, the maximum grade per patient was calculated (worst ever by patient). AE grades according to CTCAE v3.0, Common Terminology Criteria for Adverse Events version 3.0. p* = significance level for grade 2, 3 and 4; p# = significance level for grade 3 and 4.

Adverse events at 36 months after randomisation CTRT n=258; RT n=258						Adverse events at 60 months after randomisation CTRT n=141; RT n=135					
Grade 2			Grade 3-4			Grade 2			Grade 3-4		
CTRT n (%)	RT n (%)	P*	CTRT n (%)	RT n (%)	p#	CTRT n (%)	RT n (%)	P*	CTRT n (%)	RT n (%)	p#
64 (24)	48 (18)	0·03	22 (8)	16 (6)	0.31	43 (30)	30 (22)	0·03	14 (10)	8 (6)	0.27
na	na		21 (8)	16 (6)		na	na		13 (9)	8 (6)	
na	na		1 (0)	0 (0)		na	na		1 (1)	0 (0)	
1 (0)	1 (0)	1·00	1 (0)	1 (0)	1.00	4 (3)	1 (1)	0.28	2 (1)	1 (0)	1.00
1 (0)	0 (0)	0·50	0 (0)	0 (0)	1.00	0 (0)	3 (2)	0.11	0 (0)	0 (0)	1.00
15 (6)	17 (6)	0·75	5 (2)	6 (2)	1.00	10 (7)	15 (6)	0.26	3 (2)	4 (3)	0.72
3 (1)	1 (0)	0·12	2 (1)	0 (0)	0.25	3 (2)	0 (0)	0.25	0 (0)	0 (0)	1.00
11 (4)	17 (6)	0·46	2 (1)	1 (0)	0.62	14 (10)	8 (6)	0.15	2 (1)	1 (1)	1.00
4 (2)	8 (3)	0.42	1 (0)	1 (0)	1·00	6 (4)	6 (4)	1.00	0 (0)	0 (0)	1.00
0 (0)	0 (0)	0.49	1 (0)	0 (0)	0.50	2 (1)	1 (1)	0.37	2 (1)	0 (0)	0.50
3 (1)	2 (1)	1·00	1 (0)	2 (1)	1.00	4 (3)	5 (4)	0.77	0 (0)	0 (0)	1.00
3 (1)	2 (1)	1·00	1 (0)	2 (1)	1.00	3 (2)	4 (3)	0.74	0 (0)	0 (0)	1.00
17 (7)	2 (1)	<0·001	3 (1)	0 (0)	0.12	12 (8)	0 (0)	<0·001	1 (1)	0 (0)	1.00
3 (1)	2 (1)	0·45	1 (0)	0 (0)	0.50	1 (1)	0 (0)	0.50	1 (1)	0 (0)	1.00
17 (7)	1 (0)	<0·001	3 (1)	0 (0)	0.12	11 (8)	0 (0)	<0·001	1 (1)	0 (0)	1.00
17 (7)	15 (6)	0·24	4 (2)	0 (0)	0.06	11 (8)	5 (4)	0.27	3 (2)	3 (2)	1.00
2 (1)	5 (2)	0·72	1 (0)	0 (0)	0.50	5 (4)	2 (1)	0.34	2 (1)	1 (1)	1.00
0 (0)	3 (1)	0.25	0 (0)	0 (0)	1.00	1 (1)	1 (1)	0.61	0 (0)	1 (1)	0.50
4 (2)	3 (1)	0·50	1 (0)	0 (0)	0.50	0 (0)	2 (1)	0.11	0 (0)	1 (1)	0.50
4 (2)	1 (0)	0.12	1 (0)	0 (0)	0.50	2 (1)	0 (0)	0.12	2 (1)	0 (0)	0.50
1 (0)	0 (0)	1.00	0 (0)	1 (0)	1·00	2 (1)	0 (0)	0.25	0 (0)	0 (0)	1.00
8 (3)	3 (1)	0·09	1 (0)	0 (0)	0.50	7 (5)	7 (5)	1.00	0 (0)	0 (0)	1.00
0 (0)	0 (0)	1.00	0 (0)	1 (0)	1.00	0 (0)	0 (0)	1.00	0 (0)	0 (0)	1.00
7 (3)	4 (2)	0·38	0 (0)	0 (0)	1.00	8 (6)	1 (1)	0.04	0 (0)	0 (0)	1.00





Chapter 6

Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised, phase 3 trial

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The Lancet Oncology, 2019 Sept; 20(9): 1273-1285

ABSTRACT

Background

The PORTEC-3 trial investigated the benefit of combined adjuvant chemotherapy and radiotherapy versus pelvic radiotherapy alone for women with high-risk endometrial cancer. We updated the analysis to investigate patterns of recurrence and did a post-hoc survival analysis.

Methods

In the multicentre randomised phase 3 PORTEC-3 trial, women with high-risk endometrial cancer were eligible if they had International Federation of Gynaecology and Obstetrics (FIGO) 2009 stage I, endometrioid grade 3 cancer with deep myometrial invasion or lymphovascular space invasion, or both; stage II or III disease; or stage I–III disease with serous or clear cell histology; were aged 18 years and older; and had a WHO performance status of 0–2. Participants were randomly assigned (1:1) to receive radiotherapy alone (48.6 Gy in 1.8 Gy fractions given on 5 days per week) or chemoradiotherapy (two cycles of cisplatin 50 mg/m^2 given intravenously during radiotherapy, followed by four cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2 given intravenously), by use of a biased coin minimisation procedure with stratification for participating centre, lymphadenectomy, stage, and histological type. The co-primary endpoints were overall survival and failure-free survival. Secondary endpoints of vaginal, pelvic, and distant recurrence were analysed according to the first site of recurrence. Survival endpoints were analysed by intention-to-treat, and adjusted for stratification factors. Competing risk methods were used for failure-free survival and recurrence. We did a post-hoc analysis to analyse patterns of recurrence with 1 additional year of follow-up. The study was closed on Dec 20, 2013; follow-up is ongoing. This study is registered with ISRCTN, number ISRCTN14387080, and ClinicalTrials.gov, number NCT00411138.

Findings

Between Nov 23, 2006, and Dec 20, 2013, 686 women were enrolled, of whom 660 were eligible and evaluable (330 in the chemoradiotherapy group, and 330 in the radiotherapy-alone group). At a median follow-up of 72.6 months (IQR 59.9–85.6), 5-year overall survival was 81.4% (95% CI 77.2–85.8) with chemoradiotherapy versus 76.1% (71.6–80.9) with radiotherapy alone (adjusted hazard ratio [HR] 0.70 [95% CI 0.51–0.97], p=0.034), and 5-year failure-free survival was 76.5% (95% CI 71.5–80.7) versus 69.1% (63.8–73.8; HR 0.70 [0.52–0.94], p=0.016). Distant metastases were the first site of recurrence in most patients with a relapse, occurring in 78 of 330 women (5-year probability 21.4%; 95% CI 17.3–26.3) in the chemoradiotherapy group versus 98 of 330 (5-year probability 29.1%; 24.4–34.3) in the radiotherapy-alone group (HR 0.74 [95% CI 0.55–0.99]; p=0.047).

Isolated vaginal recurrence was the first site of recurrence in one patient (0.3%; 95% CI 0.0–2.1) in both groups (HR 0.99 [95% CI 0.06–15.90]; p=0.99), and isolated pelvic recurrence was the first site of recurrence in three women (0.9% [95% CI 0.3–2.8]) in the chemoradiotherapy group versus four (0.9% [95% CI 0.3–2.8]) in the radiotherapy-alone group (HR 0.75 [95% CI 0.17–3.33]; p=0.71). At 5 years, only one grade 4 adverse event (ileus or obstruction) was reported (in the chemoradiotherapy group). At 5 years, reported grade 3 adverse events did not differ significantly between the two groups, occurring in 16 (8%) of 201 women in the chemoradiotherapy group versus ten (5%) of 187 in the radiotherapy-alone group (p=0.24). The most common grade 3 adverse event was hypertension (in four [2%] women in both groups). At 5 years, grade 2 or worse adverse events were reported in 76 (38%) of 201 women in the chemoradiotherapy group versus 43 (23%) of 187 in the radiotherapy-alone group (p=0.002). Sensory neuropathy persisted more often after chemoradiotherapy than after radiotherapy alone, with 5-year rates of grade 2 or worse neuropathy of 6% (13 of 201 women) versus 0% (0 of 187). No treatment-related deaths were reported.

Interpretation

This updated analysis shows significantly improved overall survival and failure-free survival with chemoradiotherapy versus radiotherapy alone. This treatment schedule should be discussed and recommended, especially for women with stage III or serous cancers, or both, as part of shared decision making between doctors and patients. Follow-up is ongoing to evaluate long-term survival.

Funding

Dutch Cancer Society, Cancer Research UK, National Health and Medical Research Council, Project Grant, Cancer Australia Grant, Italian Medicines Agency, and the Canadian Cancer Society Research Institute.

INTRODUCTION

Women with endometrial cancer generally have a favourable prognosis;[1] only about 15–20% have high-risk disease characteristics with an increased incidence of distant metastases and cancer-related death.[2–4] High-risk endometrial cancer is defined as endometrioid endometrial cancer stage I, grade 3 with deep invasion, stage II or III endometrioid endometrial cancer (no residual disease), or non-endometrioid (serous or clear cell) histology.[1]

Women with high-risk endometrial cancer have been treated with pelvic external-beam radiotherapy for several decades. Findings of clinical trials comparing adjuvant chemotherapy alone with external-beam radiotherapy alone have shown no differences in survival outcomes.[5,6] Because a higher incidence of pelvic relapses has been reported with chemotherapy alone compared with a treatment schedule including external-beam radiotherapy,[7,8] the combination of external-beam radiotherapy with chemotherapy has been explored in clinical trials.

The randomised phase 3 PORTEC-3 trial was initiated to investigate the benefit of a combined adjuvant chemotherapy and radiotherapy (chemoradiotherapy) schedule compared with external-beam radiotherapy alone for women with high-risk endometrial cancer. Previously reported efficacy results with a time-based analysis and a median follow-up of 60.2 months (IQR 48.1–73.1) showed a significant 7% improvement in failure-free survival for patients treated with chemoradiotherapy compared with those treated with radiotherapy alone (76% vs 69% at 5 years) without a significant difference in overall survival (82% vs 77% at 5 years).[9] In a subgroup analysis, the largest failure-free survival benefit with chemoradiotherapy (11%; 69% vs 58% at 5 years) was observed in women with stage III disease, who have a higher baseline risk of recurrence than women with stage I–II disease.

The aim of the present analysis of the PORTEC-3 trial is to present the patterns of recurrence, treatment, and survival after recurrence and an updated (post-hoc) analysis of the primary endpoints with prolonged follow-up.

METHODS

Study design and participants

PORTEC-3 was an open-label, multicentre, randomised intergroup phase 3 trial led by the Dutch Gynaecological Oncology Group (DGOG). The trial was done at 103 centres (oncology centres, university hospitals, regional hospitals, or radiation oncology centres with referrals from regional hospitals) in six clinical trial groups collaborating in the Gynaecological Cancer Intergroup. Participating groups were the National Cancer

Research Institute (NCRI; UK), the Australia and New Zealand Gynaecologic Oncology Group (ANZGOG; Australia and New Zealand), the Mario Negri Gynaecologic Oncology Group (MaNGO; Italy), the Canadian Cancer Trials Group (Canadian Cancer Trials Group; Canada), and Fedegyn (France).

Details about patient selection and treatment have been published previously.[9,10] All patients first underwent surgery. In brief, surgery consisted of total abdominal or laparoscopic hysterectomy and bilateral salpingooophorectomy. The extent of lymph node removal was left to the discretion of the participating centres, although pelvic lymph node debulking and para-aortic lymph node sampling were recommended in case of macroscopic positive pelvic nodes or para-aortic nodes, or both. Full surgical staging (including omentectomy, peritoneal biopsies, and lymph node sampling) was recommended for patients with serous or clear cell cancer. FIGO 2009 staging was assigned on the basis of surgical and pathological findings. Central pathology review was mandatory before randomisation to confirm eligibility for study entry.[11]

Eligible patients were women with histologically confirmed endometrioid endometrial cancer with either International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IA grade 3 with documented lymphovascular space invasion; stage IB grade 3 disease; stage II disease; stage IIIA, IIIB (parametrial invasion), or IIIC disease; or stage IA–III with serous or clear cell histology (IA with invasion). Eligibility criteria also included WHO performance score 0–2; adequate bone marrow function (white blood cell count $\geq 3.0 \times 10^9$ cells per L, platelets $\geq 100 \times 10^9$ per L), liver function (bilirubin $\leq 1.5 \times$ upper limit of normal, aspartate aminotransferase to alanine aminotransferase ratio $\leq 2.5 \times$ upper limit of normal) and kidney function (creatinine clearance >60 mL/min calculated according to Cockroft and Gault or >50 mL/min edetic acid [EDTA] clearance), and age 18 years or older (without an upper age limit, because elderly women might benefit from the study treatment if they were deemed fit enough to undergo chemotherapy). Exclusion criteria were uterine sarcoma or carcinosarcoma, previous malignancy (except for non-melanomatous skin cancer) within the past 10 years, previous pelvic radiotherapy, previous hormonal therapy or chemotherapy, bulky cervical involvement with radical hysterectomy, inflammatory bowel disease, residual macroscopic tumour, impaired renal or cardiac function, neuropathy grade 2 or worse, hearing impairment grade 3 or worse, or a congenital hearing disorder.

Written informed consent was obtained from all patients. The protocol was approved by the Dutch Cancer Society and by the ethics committees of all participating groups. The study protocol is available online (http://www.msbi.nl/portec3).

Randomisation and masking

Patients were randomly assigned (1:1) to open-label treatment groups with chemoradiotherapy or radiotherapy alone, by use of a biased-coin minimisation procedure en-

suring balance overall and within each stratum of the stratification factors (participating centre), lymphadenectomy [yes vs no], FIGO 2009 stage of cancer [IA vs IB vs II vs III]), and histological type [endometrioid carcinoma vs serous or clear cell carcinoma]). Patients were registered and randomly assigned by the data centres of the participating groups and treatment was assigned with a web-based application. Participants, physicians, and investigators were not masked to treatment allocation.

Procedures

External-beam pelvic radiotherapy was given to patients in both treatment groups to a total dose of 48.6 Gy in 1.8 Gy fractions, 5 days per week. Specifications of the treatment schedule have been reported previously.[9–11] In case of glandular or stromal cervical involvement, or both, a brachytherapy boost was given. Brachytherapy dose was equivalent to 14 Gy in 2 Gy fractions (with a recommended scheme of 10 Gy high-dose rate in fractions of 5 Gy). Treatment was recommended to start within 4–6 weeks of surgery, but no later than 8 weeks after surgery. Overall radiotherapy treatment time was not to exceed 50 days.

In the chemoradiotherapy group, women received two cycles of cisplatin 50 mg/m^2 administered intravenously in the first and fourth week of external-beam radiotherapy, followed by four cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2 administered intravenously at 21-day intervals. This schedule was based on the RTOG-9708 trial,[12] with substitution of cisplatin by carboplatin in the adjuvant phase. Adjuvant chemotherapy was started within 3 weeks after completion of external-beam pelvic radiotherapy, and with a 28-day interval from the second concurrent cycle. Cisplatin was postponed for 1 week in the event of haematological, renal, or other toxicities or discontinued if recovery required more than 1 week or in the case of grade 2 or worse neuropathy. Carboplatin was postponed or stopped in case of severe haematological toxicity. Paclitaxel was postponed if grade 2 neuropathy developed and stopped if recovery exceeded 1 week or if grade 3 neuropathy developed. Details about chemotherapy stopping rules have been described previously.[10]

Follow-up was focused on patient history and pelvic examination to detect adverse events (grade ≥2 according to Common Terminology Criteria for Adverse Events [CTCAE] version 3.0) and symptoms of recurrent disease, with annual chest radiographs, blood counts, and chemistry tests (including CA-125) until 5 years after randomisation. Long-term follow-up of vital status and events was required at 7 years and 10 years. Health-related quality-of-life assessments were done at baseline, at the end of radiotherapy, at 6-month intervals from randomisation until 24 months, and at 36 and 60 months.

Patients who immediately withdrew informed consent after randomisation without any information were excluded from the analysis, as were patients who were ineligible for the study. There were no other criteria for a patient to be removed from the study.

Outcomes

The co-primary endpoints were overall survival and failure-free survival. Overall survival was defined as the time from randomisation to death from any cause. Failure-free survival was defined as the time from randomisation to any relapse, or death related to endometrial cancer or treatment, whichever occurred first. Women who were alive were censored at the date of their last follow-up. Secondary endpoints were vaginal, pelvic, or distant recurrence; treatment-related toxicity; and health-related quality of life.[10] Recurrences were analysed according to first site of recurrence as well as the total number of recurrences. Simultaneous vaginal and pelvic recurrence was considered pelvic recurrence; and simultaneous vaginal, pelvic, and distant recurrence was considered distant recurrence. Abdominal recurrences outside the pelvic area (peritoneal carcinomatosis, liver, and para-aortic lymph nodal metastases) were considered distant metastases, with specification of site. After diagnosis of any relapse, treatment information was required and follow-up continued according to protocol guidelines. An extensive update on quality of life will be reported separately in a future publication.

Statistical analysis

The PORTEC-3 trial was powered (80%) to detect a 10% difference in 5-year overall survival between the treatment groups (increase from 65% to 75%; hazard ratio [HR] 0.67), with a two-sided test at an α level of 0.05. 198 overall survival events were required, with a minimum of 655 patients. A prespecified interim analysis was done in September, 2013, after 48 overall survival events (a third of the required events) had occurred. The final analysis of the co-primary endpoints was published in February, 2018, with permission of the data and safety monitoring board as a time-based analysis rather than an event-based analysis since a median follow-up of 60.2 months had been reached and because the event rate was lower than expected.

To maintain an overall α of 0.05 with a nominal α level for the interim analysis of 0.0002, the final analysis was done with a nominal α of 0.0498. The final time-based analysis was done with a correlation of 0.7859 between the test statistics of the coprimary endpoints overall survival and failure-free survival (based on 136 overall survival events and 186 failure-free survival events), and a nominal α of 0.0309 was used for each of the analyses, resulting in an overall α level of 0.0498.[13] The sequential rejection principle14 implies that if the null hypothesis of no treatment difference for one of the co-primary endpoints is rejected ($p<0.0309$), the null hypothesis of no treatment difference for the other co-primary endpoint can then be assessed at the 0.05 level, while still retaining a family-wise error rate of 0.05.

The current analysis was done to evaluate patterns of recurrences, together with a non-prespecified post-hoc analysis of survival after recurrence as well as an updated analysis

of overall survival and failure-free survival with prolonged follow-up and 5-year adverse events. Final database lock was on Nov 29, 2018.

We did statistical analyses using SPSS, version 23.0.0.2, and R, version 3.5.1. All analyses were done by intention to treat, excluding ineligible patients and those who immediately withdrew informed consent after randomisation. Differences in relapse and survival rates between the groups were tested with the log-rank test and Cox regression analysis. The analysis of the primary endpoints was adjusted for the stratification factors (participating group, lymphadenectomy, stage of cancer, and histological type), since a stratified minimisation procedure was used at randomisation.[15,16]

For the adjusted analysis, stratification factors were included as covariates in the Cox model. The proportional hazards assumption for treatment was checked by use of Schoenfeld residuals for overall survival and failure-free survival, and was not found to be violated.[17] Patient characteristics were compared with a χ^2 test. Survival after recurrence was compared with a log-rank test and for this analysis the first site of recurrence was used. Competing risk methods were used for analysis of failure-free survival and recurrence, by calculating cumulative incidences and Fine-Gray regression.[18] For failure-free survival, intercurrent death was used as a competing risk. For the first failure analysis of recurrences, all other recurrences and death were used as competing risks. Median survival after recurrence was calculated as the first timepoint at which the Kaplan-Meier curve was below 50% survival. The IQR was calculated similarly. In the multivariable analysis, the following covariates were included together with treatment: stage, histological type and grade, type of surgery, participating groups, lymphovascular space invasion, and age. The median follow-up and IQR was estimated with the reverse Kaplan-Meier method.

This study is registered with ISRCTN, number ISRCTN14387080, and ClinicalTrials.gov, number NCT00411138.

Role of the funding source

The funders of the study had no role in study design, data collection, data interpretation, data analysis, or writing of this report. The central data manager (KWV), the chief investigator (CLC), the associated investigators (SMdB and RAN), and the trial statistician (HP) had full access to all the data. The decision to submit for publication was made after discussion within the trial management group. The corresponding author and chief investigator had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between Nov 23, 2006, and Dec 20, 2013, 686 women were enrolled and randomly assigned to chemoradiotherapy (n=343) or radiotherapy (n=343); 26 patients were excluded after randomisation (figure 1), resulting in 660 patients in the intention-to-treat analysis (330 in each group). Median follow-up was 72.6 months (IQR 59.9–85.6) at the time of the current analysis and 75% of participants had reached at least 5 years of follow-up.

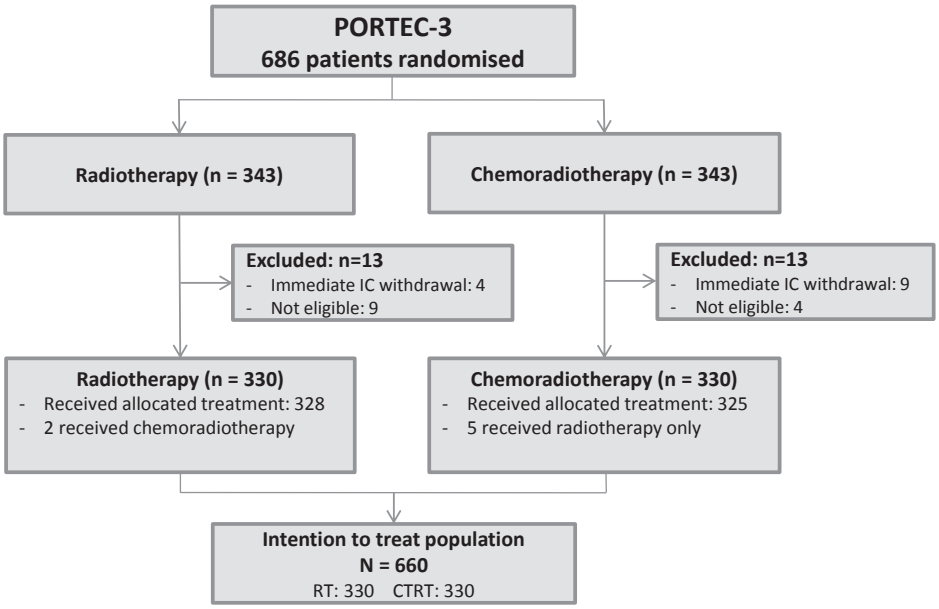

Figure 1. Trial profile

Patient characteristics were well balanced between the treatment groups (table 1). The median age of the enrolled patients was 62 years (IQR 56–68). Baseline characteristics of patients with and without a recurrence are given in table 1.

Radiotherapy was completed in 329 (>99%) of 330 women in the chemoradiotherapy group and in 325 (99%) of 330 in the radiotherapy alone group. Vaginal brachytherapy was given to 309 (47%) of 660 patients: 151 (46%) of 330 patients on chemoradiotherapy and 158 (48%) of 330 on radiotherapy alone. In the chemoradiotherapy group, concurrent cisplatin was completed by 304 (92%) of 330 women, adjuvant carboplatin by 262 (79%), and adjuvant paclitaxel by 233 (71%). At least one dose reduction of cisplatin (to 40 mg/m^2) was recorded for five (2%) patients, of carboplatin (from AUC5 to AUC4) for 36 (11%) patients, and of paclitaxel (from 175 mg/m^2 to 135 mg/m^2) for 50 (15%) patients. Chemotherapy was

Table 1. Baseline characteristics, by treatment group and by recurrence status

	Chemoradiotherapy (n = 330)		Radiotherapy (n = 330)		Any recurrence (n = 185)		No recurrence (n = 475)		p-value[$]
Age at randomisation, years									
Median	62·4		62·0		63·9		60·9		
Interquartile range	56·5-67·9		55·8-68·2		59·0-69·9		55·5-67·6		
< 60 years	128	39%	140	42%	54	29%	214	45%	<0·0001
60-69 years	144	44%	128	39%	86	47%	186	39%	
≥70 years	58	18%	62	19%	45	24%	75	16%	
FIGO 2009 stage									
Stage IA	39	12%	39	12%	14	8%	64	14%	<0·0001
Stage IB	59	18%	58	18%	22	12%	95	20%	
Stage II	80	24%	90	27%	42	23%	128	27%	
Stage IIIA	46	14%	37	11%	22	12%	61	13%	
Stage IIIB	18	6%	24	7%	19	10%	23	5%	
Stage IIIC	88	27%	82	25%	66	36%	104	22%	
Histologic grade and type									
EEC* Grade 1/2	127	39%	131	40%	61	33%	197	42%	<0·0001
EEC* Grade 3	107	32%	106	32%	59	32%	154	32%	
Serous	53	16%	52	16%	47	25%	58	12%	
Clear cell	29	9%	33	10%	17	9%	45	10%	
Other	14	4%	8	2%	1	1%	21	4%	
Myometrial invasion									
<50%	116	35%	123	37%	53	29%	186	39%	0·010
≥50%	212	65%	206	63%	132	71%	286	61%	
Missing	2		1		0		3		
LVSI									
Present	197	60%	192	58%	124	67%	265	56%	0·008
Absent	133	40%	138	42%	61	33%	210	44%	
WHO performance									
0 - 1	323	98%	324	98%	181	98%	466	99%	
≥2	5	2%	5	2%	4	2%	6	1%	
Missing	2		1		0		3		
Type of surgery									
TAH and BSO	97	29%	97	29%	58	31%	136	29%	0·866
TAH and BSO plus LND or full staging	141	43%	132	40%	72	39%	201	42%	
TLH and BSO	45	14%	42	13%	25	14%	62	13%	
TLH and BSO plus LND or full staging	47	14%	59	18%	30	16%	76	16%	

$: chi square test of variables between patients with and without any recurrence.

*: endometrioid endometrial carcinoma including mixed tumours <25% of serous or clear cell component.

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics; EEC, Endometrioid Endometrial Carcinoma; LVSI, lymph vasculair space invasoin; WHO, World Health Organisation performance score; TAH/BSO, total abdominal hysterectomy and bilateral salpingo-oopherectomy; TLH/BSO, total laparoscopic hysterectomy and bilateral salpingo-oopherectomy; LND, lymph node dissection. Missing values are not taken into account for the percentages.

discontinued in 61 (18%) of 330 patients: because of toxicity in 31 (9%), the patient's decision in 20 (6%), disease progression in seven (2%), and for other reasons in three (1%).[9,10]

At the final database lock (Nov 29, 2018), 150 patients had died (65 in the chemoradiotherapy group and 85 in the radiotherapy alone group) and 189 patients had a failure-free survival event (84 in the chemoradiotherapy group and 105 in the radiotherapy alone group). This number of events comprised 76% (150 of 198) of required overall survival events and 95% (189 of 198) of failure-free survival events for the final analysis. Most deaths were related to endometrial cancer: 53 (82%) of 65 in the chemoradiotherapy group versus 76 (89%) of 85 in the radiotherapy group. Among women assigned to chemoradiotherapy, other causes of death were second cancers (in five [8%] patients), other intercurrent disease (in three [5%] patients), and complications of treatment for metastatic disease (in two [3%] patients). Among women assigned to radiotherapy alone, other causes of death were second cancers (in five [6%] patients), other intercurrent disease (in one [1%] patient), and complications of treatment for metastatic disease (in one [1%] patient). The cause of death was uncertain for two patients treated with chemoradiotherapy and two patients treated with radiotherapy alone; these deaths were considered failure-free survival events since a relation to endometrial cancer or to treatment for endometrial cancer could not be excluded.[9]

Estimated 5-year overall survival adjusted for stratification factors was 81.4% (95% CI 77.2–85.8) with chemoradiotherapy versus 76.1% (71.6–80.9) with radiotherapy alone (HR 0.70 [95% CI 0.51–0.97], p=0.034). Estimated 5-year failure-free survival adjusted for stratification factors was 76.5% (95% CI 71.5–80.7) with chemoradiotherapy versus 69.1% (63.8–73.8) with radiotherapy alone (HR 0.70 [95% CI 0.52–0.94], p=0.016; figure 2).

In our post-hoc exploratory analysis of survival outcomes by disease stage, women with stage III disease had significantly lower overall survival and failure-free survival than women with stage I–II disease, irrespective of treatment received (appendix Figure S4). In women with stage III endometrial cancer, 5-year overall survival was 78.5% (95% CI 72.2–85.4) with chemoradiotherapy versus 68.5% (61.2–76.7) with radiotherapy alone (HR 0.63 [95% CI 0.41–0.99]; p=0.043), and 5-year failure-free survival was 70.9% (95% CI 62.9–77.4) with chemoradiotherapy versus 58.4% (49.8–66.0) with radiotherapy alone (HR 0.61 [95% CI 0.42–0.89]; p=0.011; figure 3A, B). In women with stage I–II disease, 5-year overall survival was 83.8% (95% CI 78.4–89.5) with chemoradiotherapy versus 82.0% (95% CI 76.5–87.7) with radiotherapy alone (HR 0.83 [95% CI 0.51–1.35]; p=0.45), and 5-year failure-free survival was 81.3% (95% CI 74.7–86.3) with chemoradiotherapy

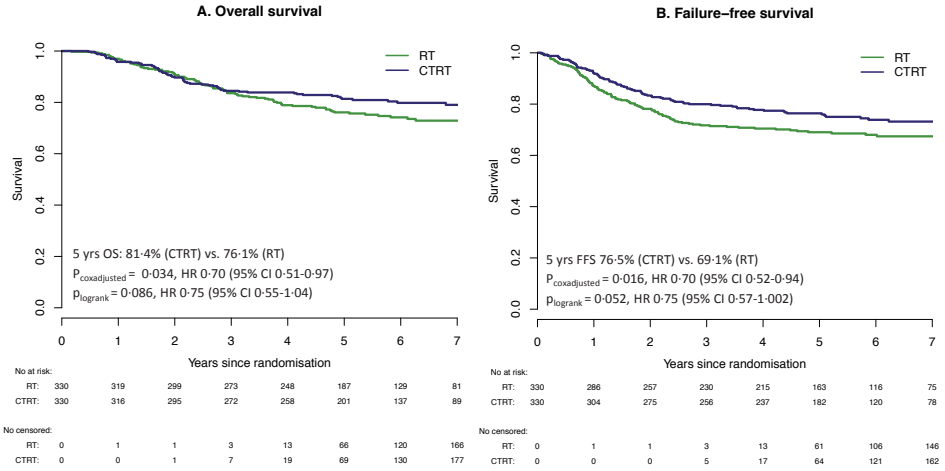

Figure 2. Kaplan-Meier survival curves for overall survival (A) and failure free survival (B) in all patients.

versus 77.3% (95% CI 70.5–82.7) with radiotherapy alone (HR 0.86 [95% CI 0.55–1.34]; p=0.51; appendix Figure S5).

When comparing serous cancers with all other histologies in a post-hoc exploratory subgroup analysis, women with serous cancers had significantly lower overall survival and failure-free survival than did those with other histologies irrespective of treatment received (appendix Figure S4), and the difference in overall survival and failure-free survival among the different disease stages was more pronounced for serous cancers than for other histologies (appendix Figure S6). After adjusting for stratification factors, significant improvements in overall survival and failure-free survival were observed for serous cancers treated with chemoradiotherapy versus radiotherapy alone: 5-year overall survival was 71.4% (95% CI 60.1–84.7) with chemoradiotherapy versus 52.8% (40.6–68.6) with radiotherapy alone (HR 0.48 [95% CI 0.24–0.96]; p=0.037), and 5-year failure-free survival was 59.7% (95% CI 45.1–71.6) with chemotherapy versus 47.9% (33.9–60.6) with radiotherapy alone (HR 0.42 [95% CI 0.22–0.80]; p=0.008; figure 3C, 3D). Stage, histological type and grade, type of surgery, participating groups, lymphovascular space invasion, and age were included in the prespecified multivariable analysis for overall and failure-free survival. Compared with radiotherapy alone, chemoradiotherapy significantly improved overall and failure-free survival in the presence of these factors (appendix Table S3). Most factors, except for lymphadenectomy (and lymphovascular space invasion for overall survival) were correlated with overall survival and failure- free survival (appendix Table S3). In a post-hoc analysis of survival outcomes by type of surgery, the type of surgery (laparotomy vs laparoscopy) did not affect overall survival or failure-free survival (appendix Figure S8).

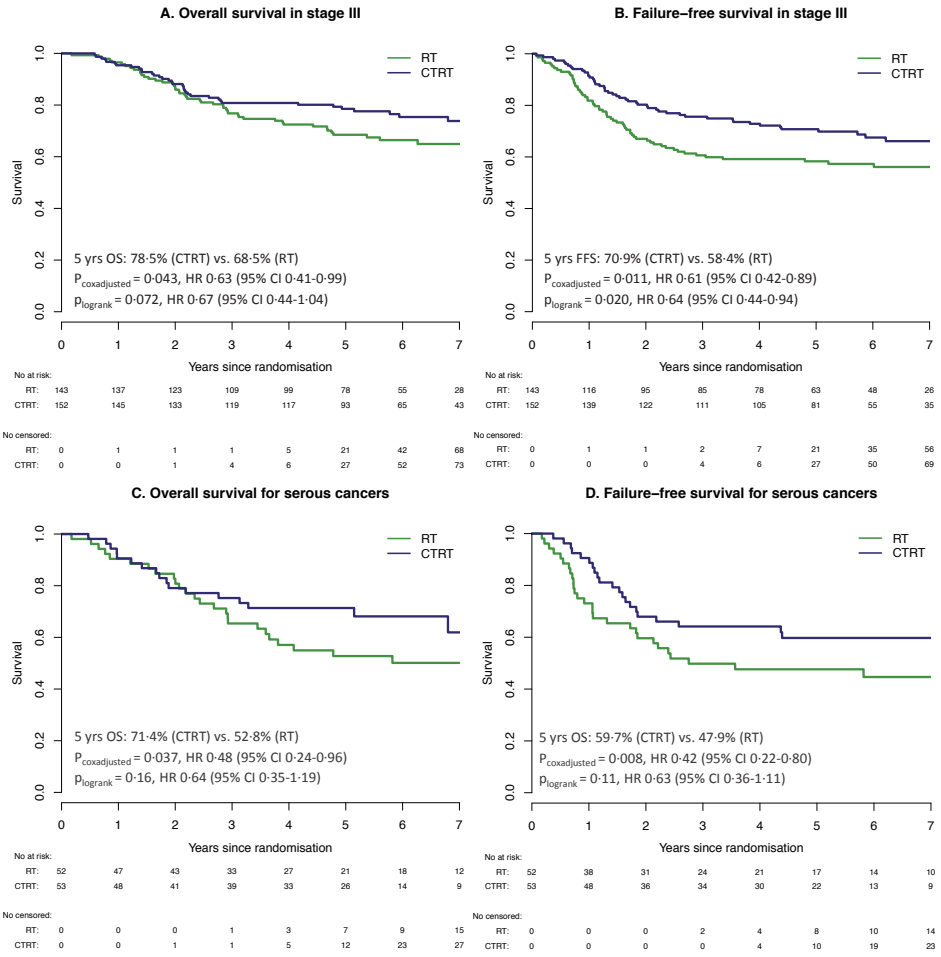

Figure 3. Kaplan-Meier survival curves for overall survival and failure-free survival among patients with stage III endometrial cancer (A and B), and for patients with serous cancer (C and D).

Distant metastases were the first type of recurrence in most patients with a recurrence, and occurred in 98 of 330 patients (5-year probability 29.1% [95% CI 24.4–34.3] in the radiotherapy-only group compared with 78 of 330 patients (5-year probability 21.4% [17.3–26.3] in the chemoradiotherapy group (HR 0.74 [95% CI 0.55–0.99]; p=0.047; table 2). In the radiotherapy group, 74 (76%) of these 98 recurrences were distant recurrence only (of which 12 were isolated para-aortic nodal recurrences); 20 patients had combined distant and pelvic recurrences (including two with distant, pelvic, and vaginal recurrences), and four had combined distant and vaginal recurrences. In the chemoradiotherapy group, 63 (81%) of 78 distant recurrences were distant only (of which nine were isolated para-aortic nodal recurrences); 11 were combined distant and

Table 2. Recurrence outcome by treatment group

	Number of events	5-year probability (95% CI)	Hazard ratio (95% CI)	Log-rank p value#
Vaginal recurrence (first recurrence)				
Chemoradiotherapy	1	0.3% (0.0-2.1)	0.99 (0.06 - 15.90)	0.99
Radiotherapy	1	0.3% (0.0-2.1)		
Pelvic recurrence (first recurrence)				
Chemoradiotherapy	3	0.9% (0.3-2.8)	0.75 (0.17 - 3.33)	0.71
Radiotherapy	4	0.9% (0.3-2.8)		
Distant metastases (first recurrence)				
Chemoradiotherapy	78	21.4% (17.3-26.3)	0.74 (0.55 - 0.996)	0.047
Radiotherapy	98	29.1% (24.4-34.3)		
Vaginal recurrence (total)				
Chemoradiotherapy	8	2.1% (1.0-4.4)	0.99 (0.37 - 2.65)	0.99
Radiotherapy	8	2.1% (1.0-4.4)		
Pelvic recurrence (total)				
Chemoradiotherapy	20	5.5% (3.5-8.6)	0.63 (0.36 - 1.11)	0.11
Radiotherapy	31	8.5% (5.9-12.1)		
Distant metastases (total)				
Chemoradiotherapy	80	22.1% (17.9-27.0)	0.75 (0.56 - 1.01)	0.057
Radiotherapy	99	29.4% (24.7-34.6)		

unadjusted for stratification factors.

pelvic recurrences (including one with distant, pelvic, and vaginal recurrence), and four were combined distant and vaginal recurrences.

Isolated vaginal recurrence was the first site of recurrence in one patient (0.3% [95% CI 0.0–2.1]) in both groups (HR 0.99 [95% CI 0.06–15.90]; p=0.99), and isolated pelvic recurrence was the first site of recurrence in four women (0.9% [0.3–2.8]) in the radiotherapy group and in three (0.9% [0.3–2.8]) in the chemoradiotherapy group (HR 0.75 [95% CI 0.17–3.33]; p=0.71; table 2).

Figure 4 shows recurrences by cancer stage and histological type. Recurrences were highest in women with stage IIIB (19 [45.2%] of 42) and stage IIIC (66 [38.8%] of 170) disease. Across the different histological types, the greatest risk of recurrence was for serous cancers (47 [44.8%] of 105), followed by clear cell cancers (17 [27.4%] of 62) and grade 3 endometrioid endometrial cancer (59 [27.7%] of 213).

Median survival after recurrence was 1.4 years (IQR 0.5–3.7) in the total PORTEC-3 cohort and did not differ significantly between the two treatment groups: 1.4 years (0.7–3.7) for patients in the radiotherapy group and 1.2 years (0.4–8.9) in the chemoradiotherapy group (HR 1.06 [95% CI 0.75–1.51]; p=0.72; table 3). In both groups, about 9–10% of patients (n=33; 16 in the radiotherapy group and 17 in the chemoradiotherapy group)

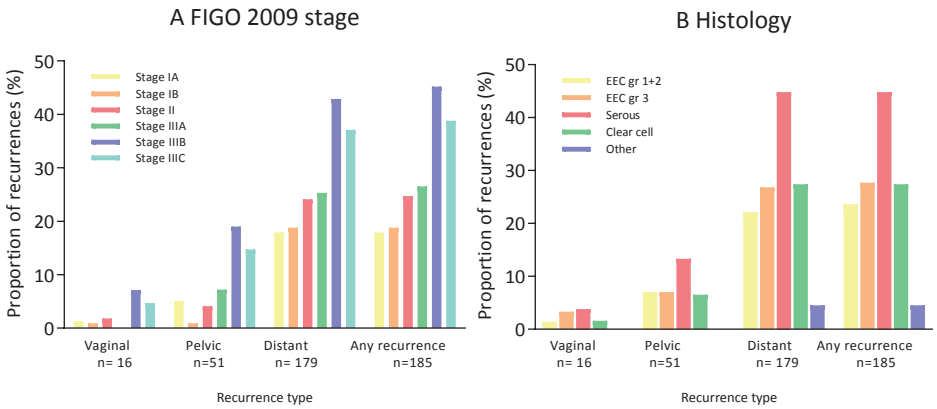

Figure 4. Recurrences divided by stage (A) and histology (B). Descriptive percentages of all recurrences are given within the different subgroups. Abbreviations: EEC, endometrioid endometrial cancer; FIGO= International Federation of Gynaecology and Obstetrics.

survived for several years after recurrence (appendix Figure S7). In these cases, recurrences were more often solitary metastases and low grade in type, and more often treated with hormonal therapy (data not shown).

In terms of treatment after recurrence, patients in the radiotherapy group were more likely to be treated with chemotherapy for their first recurrence than those in the chemoradiotherapy group (48 [47%] of 103 women vs 30 [37%] of 82 women), and most women in the radiotherapy group (43 [90%] of 48) received carboplatin plus paclitaxel (details of treatment received by the other five women are provided in the appendix (Table S1). In the chemoradiotherapy group, various combinations of chemotherapy agents were used (data not shown) and only 12 (40%) of 30 patients received carboplatin plus paclitaxel again (details of treatment received by the other 18 women are provided in the appendix Table S1). An overview of all treatment modalities is given in the appendix (Table S1 and Figure S9).

A comprehensive overview of adverse events during treatment and the first few years after treatment has been provided in previous publications.[9,10] After longer follow-up, we found no significant differences between the two treatment groups in grade 3 or worse adverse events at 12, 36, and 60 months after randomisation (appendix p 4). 60 months after randomisation, grade 3 adverse events were reported for 16 (8%) of 201 women in the chemoradiotherapy group versus ten (5%) of 187 women in the radiotherapy group (p=0.24). Only one grade 4 adverse event (ileus or obstruction) was reported (in the chemoradiotherapy group). The most frequently reported grade 3 adverse events were hypertension (in four women [2%] in both groups), any pain (in three [1%] women in the chemoradiotherapy group vs three [2%] in the radiotherapy group) and other toxicities (in three [1%] women in the chemoradiotherapy group vs two [1%] in the radiotherapy group).

Table 3. Median survival after recurrence

	No. of events	Median survival* (years; IQR)	Hazard ratio (95% CI)	Log-rank p value#
Vaginal or pelvic recurrence				
Chemoradiotherapy	4	1.2 (0.7-NR)		
Radiotherapy	6	1.4 (0.9-NR)		
Total	10	1.4 (0.9-NR)	1.31 (0.26 - 6.55)	0.74
Distant metastases				
Chemoradiotherapy	76	1.2 (0.3 - 8.9)		
Radiotherapy	93	1.5 (0.7 - 3.7)		
Total	169	1.4 (0.5-3.7)	1.05 (0.73 - 1.50)	0.79
Any recurrence				
Chemoradiotherapy	82	1.2 (0.4 - 8.9)		
Radiotherapy	103	1.4 (0.7 - 3.7)		
Total	185	1.4 (0.5-3.7)	1.06 (0.75 - 1.51)	0.72

NR= not reached. *For the survival after recurrence the first site of recurrence was used. # Log-rank p value, unadjusted for stratification factors.

At 60 months, grade 2 or worse adverse events were reported for 76 (38%) of 201 women in the chemoradiotherapy group versus 43 (23%) of 187 women in the radiotherapy group (p=0.002). Sensory neuropathy grade 2 or worse was the major difference between the two groups at 5 years, seen in 13 (6%) of 201 patients after chemoradiotherapy versus no patients in the radiotherapy group (table 4).

DISCUSSION

These updated results of the PORTEC-3 trial, with a longer median follow-up of 72 months and with 75% of participants having reached 5 years of follow-up, showed a significant improvement in both overall and failure-free survival with chemoradiotherapy versus radiotherapy alone for high-risk endometrial cancer. The absolute improvement at 5 years was 5% (HR 0.70; 95% CI 0.51–0.97) for overall survival and 7% (0.70; 0.52–0.94) for failure-free survival. Most recurrences were at distant sites, with excellent local and regional control in both groups. Women in the radiotherapy group were more likely to receive chemotherapy for their first recurrence. Women with serous cancers had worse overall survival and failure-free survival than those with other histological types, and for these women a significant improvement of overall survival (absolute improvement 19%; HR 0.48 [95% CI 0.24–0.96]) and failure-free survival (absolute improvement 12%; 0.42 [0.22–0.80]) was found with chemoradiotherapy compared with radiotherapy alone.

Table 4. Adverse events reported at 60 months after randomisation

	Grade 2			Grade 3[$]		
	Chemoradiotherapy	**Radiotherapy**	**p***	**Chemoradiotherapy**	**Radiotherapy**	**p#**
	(n=201)	(n=187)		(n=201)	(n=187)	
Any	59 (29)	33 (18)	0.002	16 (8)	10 (5)	0.24
Allergic reaction or hypersensitivity	0 (0)	0 (0)	0.48	0 (0)	1 (1)	0.48
Auditory or hearing	4 (2)	1 (1)	0.29	2 (1)	1 (1)	1.00
Fatigue	0 (0)	3 (2)	0.11	0 (0)	0 (0)	1.00
Hypertension	16 (8)	16 (9)	0.87	4 (2)	4 (2)	1.00
Lymphatics (oedema)	5 (2)	0 (0)	0.06	0 (0)	0 (0)	1.00
Gastrointestinal (any)	16 (8)	9 (5)	0.19	2 (1)	1 (1)	1.00
Constipation	3 (1)	1 (1)	1.00	0 (0)	1 (1)	1.00
Diarrhea	7 (3)	7 (4)	1.00	0 (0)	0 (0)	1.00
Ileus/obstruction	2 (1)	1 (1)	0.37	2 (1)	0 (0)	0.50
Hematological (any)	5 (2)	5 (3)	1.00	0 (0)	0 (0)	1.00
Lymphocytes	3 (1)	4 (2)	0.74	0 (0)	0 (0)	1.00
Infection (without neutropenia)	2 (1)	0 (0)	0.12	2 (1)	0 (0)	0.50
Neuropathy (any)	13 (6)	0 (0)	<0.001	1 (<1)	0 (0)	1.00
Neuropathy - motor	1 (<1)	0 (0)	0.50	1 (<1)	0 (0)	1.00
Neuropathy - sensory	12 (6)	0 (0)	<0.001	1 (<1)	0 (0)	1.00
Neurology						
other	1 (<1)	0 (0)	0.25	2 (1)	0 (0)	0.50
Pain (any)	13 (6)	5 (3)	0.15	3 (1)	3 (2)	1.00
Joint pain	7 (3)	2 (1)	0.14	2 (1)	1 (1)	1.00
Muscle pain	1 (<1)	1 (1)	0.61	0 (0)	1 (1)	0.48
Back/pelvic/limbs	0 (0)	2 (1)	0.11	0 (0)	1 (1)	0.48
Abdomen/cramps	2 (1)	0 (0)	0.12	2 (1)	0 (0)	0.50
Other	2 (1)	1 (1)	1.00	1 (<1)	1 (1)	1.00
Musculoskeletal (other)	0 (0)	1 (1)	1.00	1 (<1)	0 (0)	1.00
Genitourinary						
Incontinence	8 (4)	9 (5)	1.00	0 (0)	0 (0)	1.00
Urinary frequency	8 (4)	2 (1)	0.14	0 (0)	1 (1)	0.48
Constitutional symptoms						
Fatigue	0 (0)	3 (2)	0.11	0 (0)	0 (0)	1.00
Other	0 (0)	0 (0)	1.00	1 (<1)	0 (0)	1.00
Other toxicity	4 (2)	4 (2)	1.00	3 (1)	2 (1)	1.00

Data are n(%). [$] Only one grade 4 adverse event was reported 60 months after randomisation for a women treated in the chemoradiotherapy group (ileus or obstruction). p* = significance level: p< 0.01 for grade ≥2 events.; # = significance level: p<0.01 for grade ≥3 events. The prevalence of toxicity graded according to the Common Terminology Criteria for Adverse Events version 3.0 was calculated at each timepoint. For each adverse event, the maximum grade per patient was recorded (worst ever by patient).

External-beam radiotherapy has been the standard adjuvant treatment for women with high-risk endometrial cancer for several decades. Since trials comparing adjuvant chemotherapy alone with external-beam radiotherapy alone did not show differences in survival,[5,6] the combination of external-beam radiotherapy with four cycles of platinum-based chemotherapy was investigated in the randomised NSGO-EC-9501/EORTC-55991 trial.[19] A pooled analysis with the ManGO ILIADE-III trial showed a significant improvement in progression-free survival at 5 years with chemoradiotherapy versus radiotherapy alone (78% vs 69%, p=0.01) and a nonsignificant improvement in 5-year overall survival (82% vs 75%; p=0.07).[19] The RTOG 9708 phase 2 trial investigated combined external-beam radiotherapy with concurrent and adjuvant chemotherapy, with both treatment modalities started early after surgery.[12] This combination showed manageable toxicity and a 5-year overall survival of 85% and relapse-free survival of 79%. The PORTEC-3 trial confirmed these high survival rates in a large randomised trial, with estimated 5-year overall survival of 79% and 5-year failure-free survival of 73% in the chemoradiotherapy group.

High-risk endometrial cancer comprises a heterogeneous group of tumours with both early-stage disease with high-risk features and advanced stage endometrial cancer and non-endometrioid tumours. When analysing results by stage, women with stage III endometrial cancer had a significantly higher risk of recurrence than did those with stage I–II disease. For women with stage I–II endometrial cancer, combined adjuvant treatment yielded only a small absolute improvement of 2% (HR 0.83; 95% CI 0.51–1.35) in 5-year overall survival and of 4% (0.86; 0.55–1.34) in failure-free survival. These results are supported by the results of the Gynecologic Oncology Group (GOG)-249 trial, in which women with stage I–II endometrial cancer were randomly assigned to receive external-beam radiotherapy or vaginal brachytherapy and three cycles of carboplatin–paclitaxel chemotherapy. No differences in overall survival or recurrence-free survival were reported, but pelvic and para-aortic recurrences were significantly more frequent after vaginal brachytherapy and chemotherapy.[20] Taking the results of the GOG-249 and PORTEC-3 trials together, a minimal benefit in failure-free survival and overall survival in stage I–II endometrial cancer achieved with chemoradiotherapy does not seem to justify the increased frequency of adverse events, impaired quality of life, and longer treatment duration of combined treatment for these patients.

For women with stage III endometrial cancer in PORTEC-3, a significant improvement in overall survival (HR 0.63) and in failure-free survival (HR 0.61) was found with chemoradiotherapy versus radiotherapy alone. In the GOG-258 trial, 813 women with stage III–IVA endometrial cancer were randomly assigned to receive pelvic external-beam radiotherapy with concurrent and adjuvant chemotherapy (with the same schedule as that of the PORTEC-3 trial), or to receive chemotherapy alone (six cycles of carboplatin and paclitaxel).[21] Although no differences in recurrence-free and overall survival were

found, significantly more vaginal recurrences (HR 0.36) and pelvic or para-aortic, or both, recurrences (HR 0.43) were seen in women treated with chemotherapy alone.

While using the same chemoradiotherapy schedule as in PORTEC-3, recurrence-free survival in GOG-258 was 59% (97% stage III) compared with 71% in PORTEC-3 for stage III disease. In retrospective cohorts, a high frequency of locoregional recurrence was also found after treatment with chemotherapy alone,[7,8,22] supporting the continued use of pelvic radiotherapy in patients undergoing adjuvant chemotherapy. Taking the findings of these two recent large trials together, the addition of chemotherapy should be discussed and recommended for women with stage III endometrial cancer to improve failure-free and overall survival as part of shared decision making between doctors and their patients.

Overall and failure-free survival for women with serous cancers were lower than for those with endometrioid and clear cell cancers, and the difference in overall survival and failure-free survival among the different disease stages was more pronounced for women with serous cancers than for those with other histologies. Retrospective studies have reported improvements in overall survival and recurrence-free survival with chemotherapy for serous cancers.[23,24] In several randomised trials, however, subgroup analyses for treatment effect in different histological types did not confirm such benefits.[19,20,25] In a GOG study of four randomised chemotherapy trials in women with metastatic and recurrent endometrial cancer, comprising 1203 patients, no association was found between response and histological type.[26] In the PORTEC-3 trial, however, a significant improvement in both overall survival and failure-free survival was found for women with serous cancers treated with chemoradiotherapy. However, such subgroup analyses should be interpreted with caution for several reasons. The number of patients with serous cancer in these trials is relatively small, and serous cancers have often been grouped together with clear cell cancers. In the current PORTEC-3 analysis, we found that the frequency of recurrence among women with clear cell cancers was similar to that of women with endometrioid tumours and clearly lower than that of women with serous cancers. Another factor to consider when interpreting subgroup analyses is the use of different chemotherapy regimens among the different trials. In the NSGO/EORTC trial,[19] the GOG-122 trial,[25] and the GOG metastatic endometrial cancer analysis,[26] cisplatin-based combinations were used, whereas in the PORTEC-3, GOG-249, and GOG-258 trials, carboplatin and paclitaxel were given.

In the PORTEC-3 trial, 105 patients with serous cancers were included. PORTEC-3 is the first randomised trial to show a significant improvement in overall survival and failure-free survival with combined adjuvant treatment for women with serous cancers, but in absolute terms mostly for higher stage disease. The number of women and events are too low to report on treatment efficacy across the different stages of serous cancers. To achieve further improvements in survival outcomes for women with serous cancers,

targeted therapies based on molecular alterations should be explored. Serous cancers are characterised by a high frequency of TP53 mutations, and in approximately 25% of patients an overexpression of HER2/neu has been reported, with a potential progression-free survival benefit by addition of trastuzumab to chemotherapy.[27,28]

Most first recurrences in the PORTEC-3 trial were at distant sites, with only few simultaneous vaginal or pelvic recurrences. Isolated vaginal or pelvic recurrence was rare. This finding is in line with other randomised trials that used radiotherapy in both groups.[19,20]

In the PORTEC-3 schedule, which was based on the RTOG-9708 phase 2 trial,[12] both treatment modalities were started early after surgery, aiming at achieving rapid efficacy of both treatment modalities and potential increase of the effect of radiotherapy by the two concurrent cycles. This schedule has now been proven safe and effective in two large, randomised trials with toxicity and quality-of-life data, whereas no phase 3 evidence is available for the specific benefit for other sequences of radiotherapy and chemotherapy.[9,10,19,21] Widespread differences exist in the practice of giving chemotherapy and radiotherapy in either sequence or in a so-called sandwich schedule; concurrent start of both modalities might be most effective and efficient. Since most first recurrences were at distant sites (although with fewer in the combined treatment group than in the radiotherapy-only group), one could speculate whether multi-agent chemotherapy should already be given concurrently. However, no evidence exists for other concurrent schedules in endometrial cancer, whereas, for example, weekly carboplatin and paclitaxel has been shown to be effective in patients with oesophageal cancer.

In a patient preference study done by the ANZGOG group among their PORTEC-3 participants,[29] more than 50% of women reported a 5% survival improvement or an extra 1 year survival as being sufficient to make chemotherapy worthwhile. Although both co-primary endpoints showed a significant improvement and are within this range, weighing the benefits of chemoradiotherapy against the increased risk of adverse events remains important. Significantly more severe adverse events and reduced health-related quality of life were reported in the combined treatment group during the first year after treatment.[9,10] However, rapid recovery was seen, with no significant differences in grade 3–4 adverse events from 12 months onwards. At 60 months after randomisation, significantly more patients reported grade 2 toxicity with the combination treatment, of which sensory neuropathy is the most significant (6% vs 0%) and clinically relevant.[9,10]

A limitation of this analysis is that the subgroup analyses were not powered and the survival update was a non-prespecified, post-hoc analysis, with an additional follow-up time of 12 months after 95% of the required failure-free survival events had occurred. However, the previous (time-based) analysis already showed a significant improvement in failure-free survival, and the overall survival difference was close to significance. The differences in overall and failure-free survival have remained and have even become stronger with a longer follow-up time and more events recorded.

In terms of the statistical significance of our findings, the p value for failure-free survival was 0.016 and that for overall survival was 0.034, whereas the boundary for claiming positivity of the study based on Pocock correction was 0.031 (ie, if either or both of the p values were lower than 0.031 the study is deemed positive). The sequential rejection principle[14] implies that, since the null hypothesis of no treatment difference for failure-free survival was rejected ($p<0.031$), the null hypothesis of no treatment difference for the co-primary endpoint of overall survival can then be assessed at the 0.05 level, while still retaining a family-wise error rate of 0.05. Application of this principle implies that the treatment effect for overall survival can be considered significant.

Better selection of women for adjuvant treatment might be achieved by integration of molecular characteristics. For intermediate-risk endometrial cancer, an improved risk assessment was reported with an integrated profile of clinicopathological and molecular risk factors.[30] This approach is currently being tested in the randomised PORTEC-4a trial (NCT03469674). A pilot study of the TransPORTEC consortium showed that determination of the molecular subgroups as described by the Cancer Genome Atlas Group[27] also improved risk assessment in high-risk endometrial cancer. Translational research is being done on tumour tissue samples donated by PORTEC-3 participants as part of an international collaboration. The molecular subgroups and additional molecular characteristics will be ascertained and the benefit of adjuvant chemotherapy in relation to these factors will be explored.

In conclusion, this updated analysis of the PORTEC-3 trial shows improved 5-year overall and failure-free survival with chemoradiotherapy compared with radiotherapy alone for women with high-risk endometrial cancer, with the greatest absolute benefit for chemotherapy seen in women with stage III disease or serous cancers, or both. Most recurrences were at distant sites, suggesting that new systemic treatment approaches are needed to improve survival outcomes. Molecular analysis has the potential to improve risk stratification and should be used to identify subgroups that can derive the greatest benefit from chemotherapy and to select patients for targeted therapies; molecular studies on tissue samples donated by PORTEC-3 trial participants are ongoing.

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SUPPLEMENTARY MATERIAL

Table S1. Treatment for first recurrence

	Total		Radiotherapy		Chemoradiotherapy	
Treatment	**N**	**%**	**N**	**%**	**N**	**%**
Chemotherapy*	78	42.2%	48	46.6%	30	36.6%
Hormonal therapy	26	14.1%	13	12.6%	13	15.9%
Radiotherapy	15	8.1%	7	6.8%	8	9.8%
Surgery	11	5.9%	7	6.8%	4	4.9%
Targeted therapy	2	1.1%	0	0.0%	2	2.4%
Surgery + radiotherapy	5	2.7%	1	1.0%	4	4.9%
Surgery + hormonal therapy	2	1.1%	0	0.0%	2	2.4%
Surgery + chemotherapy	4	2.2%	3	2.9%	1	1.2%
Surgery + radiotherapy + chemotherapy	1	0.5%	1	1.0%	0	0.0%
Radiotherapy + hormonal therapy	6	3.2%	3	2.9%	3	3.7%
Radiotherapy + chemotherapy	5	2.7%	2	1.9%	3	3.7%
Chemotherapy + hormonal therapy	2	1.1%	2	1.9%	0	0.0%
Unknown	1	0.5%	1	1.0%	0	0.0%
No treatment	27	14.6%	15	14.6%	12	14.6%
Total	185	100.0%	103	100.0%	82	100.0%

* Radiotherapy group: 43 patients received carboplatin + paclitaxel; 2 carboplatin; 1 adriamycine + cisplatin; 1 paclitaxel; 1 paclitaxel, epirubicine, cisplatin). Chemoradiotherapy group: 12 patients received carboplatin + paclitaxel; 5 adriamycine + cisplatin; 4 carboplatin + doxorubicine; 3 doxorubicine; 2 carboplatin + epirubucine; 1 paclitaxel; 1 cyclophosphamide, adriamycine, cisplatin; 1 apebilone; 1 unknown.

Table S2. Late toxicity reported by physicians using the CTCAE v3.0 at 12, 36 and 60 months of follow-up.

	12 months					
	Grade 2			Grade 3/4		
	CTRT	RT	p*	CTRT	RT	p#
	(n=316)	(n=319)		(n=316)	(n=319)	
Any	103 (33)	89 (28)	0·04	33 (10)	21 (7)	0·09
Any grade 3	na	na		27 (9)	19 (6)	
Any grade 4	na	na		6 (2)	2 (1)	
Auditory or hearing	10 (3)	2 (1)	0·02	0 (0)	0 (0)	1·00
Hypertension	14 (4)	17 (5)	0·62	4 (1)	5 (2)	1·00
Lymphatics (edema)	8 (3)	3 (1)	0·11	2 (1)	1 (<1)	0·62
Any Gastrointestinal	21 (7)	19 (6)	0·24	7 (2)	2 (1)	0·11
Diarrhea	11 (3)	8 (3)	0·39	1 (<1)	1 (<1)	1·00
Ileus or obstruction	2 (1)	3 (1)	0·77	4 (1)	2 (1)	0·45
Any Hematological	26 (8)	21 (7)	0·89	4 (1)	7 (2)	0·55
Lymphocytes	24 (8)	22 (7)	0·89	4 (1)	5 (2)	1·00
Any Neuropathy	26 (8)	1 (<1)	<0·001	4 (1)	1 (<1)	0·22
Motor	1 (<1)	0 (0)	0·22	3 (1)	1 (<1)	0·37
Sensory	26 (8)	1 (<1)	<0·001	4 (1)	1 (<1)	0·22
Any Pain	26 (8)	22 (7)	0·18	8 (3)	3 (1)	0·14
Joint pain	4 (1)	3 (1)	0·72	0 (0)	0 (0)	1·00
Muscle pain	4 (1)	1 (<1)	0·22	0 (0)	0 (0)	1·00
Back, pelvic or limbs	11 (3)	5 (2)	0·05	3 (1)	1 (<1)	0·37
Abdomen or cramps	2 (1)	5 (2)	0·77	3 (1)	2 (1)	0·69
Musculoskeletal (other)	3 (1)	0 (0)	0·12	0 (0)	0 (0)	1·00
Pulmonary - dyspnea	2 (1)	2 (1)	1·00	0 (0)	1 (<1)	1·00
Genitourinary						
Incontinence	8 (3)	9 (3)	1·00	1 (<1)	1 (<1)	1·00
Obstruction	0 (0)	0 (0)	1·00	0 (0)	1 (<1)	1·00
Urinary frequency	4 (1)	8 (3)	0·26	0 (0)	1 (<1)	1·00
Constitutional						
Fatigue	5 (2)	4 (1)	1·00	0 (0)	2 (1)	0·50
Other	5 (2)	4 (1)	0·54	1 (<1)	0 (0)	0·50
Other toxicity	0 (0)	0 (0)	1·00	0 (0)	0 (0)	1·00

Data are n(%). *Abbreviations:* CTRT, combined chemotherapy and radiotherapy; RT, radiotherapy; GI, gastro-intestinal; GU, genito-urinary; CTCAE v3.0, Common Terminology Criteria for Adverse Events version 3.0; AE were calculated at each time point. Per AE, the maximum grade per patient was calculated (worst ever by patient). p* = significant level < 0.01 for grade ≥2, 3 and 4; p# = significant level <0.01 for grade 3 and 4.

36 months						60 months					
Grade 2			Grade 3/4			Grade 2			Grade 3/4		
CTRT (n=272)	RT (n=273)	p*	CTRT (n=272)	RT (n=273)	p#	CTRT (n=201)	RT (n=187)	p*	CTRT (n=201)	RT (n=187)	p#
62 (23)	49 (18)	0·06	22 (8)	16 (6)	0·32	59 (29)	33 (18)	0·002	17 (8)	10 (5)	0·24
na	na		21 (8)	17 (7)		na	na		16 (8)	10 (5)	
na	na		1 (<1)	0 (0)		na	na		1 (<1)	0 (0)	
1 (<1)	1 (<1)	1·00	1 (<1)	1 (<1)	1·00	4 (2)	1 (1)	0·29	2 (1)	1 (1)	1·00
15 (6)	17 (6)	0·75	5 (2)	6 (2)	1·00	16 (8)	16 (9)	0·87	4 (2)	4 (2)	1·00
3 (1)	1 (<1)	0·12	2 (1)	0 (0)	0·25	5 (2)	0 (0)	0·06	0 (0)	0 (0)	1·00
11 (4)	17 (6)	0·46	2 (1)	1 (<1)	0·62	16 (8)	9 (5)	0·19	2 (1)	1 (1)	1·00
4 (1)	8 (3)	0·42	1 (<1)	1 (<1)	1·00	7 (3)	7 (4)	1·00	0 (0)	0 (0)	1·00
0 (0)	0 (0)	0·50	1 (<1)	0 (0)	0·50	2 (1)	1 (1)	0·37	2 (1)	0 (0)	0·50
3 (1)	3 (1)	1·00	1 (<1)	2 (1)	1·00	5 (2)	5 (3)	1·00	0 (0)	0 (0)	1·00
3 (1)	3 (1)	1·00	2 (1)	1 (<1)	1·00	3 (1)	4 (2)	0·74	0 (0)	0 (0)	1·00
17 (6)	2 (1)	<0·001	3 (1)	0 (0)	0·12	13 (6)	0 (0)	<0·001	1 (<1)	0 (0)	1·00
3 (1)	2 (1)	0·45	1 (<1)	0 (0)	0·50	1 (<1)	0 (0)	0·50	1 (<1)	0 (0)	1·00
17 (6)	1 (<1)	<0·001	3 (1)	0 (0)	0·12	12 (6)	0 (0)	<0·001	1 (<1)	0 (0)	1·00
17 (6)	15 (5)	0·24	4 (1)	0 (0)	0·06	13 (6)	5 (3)	0·15	3 (1)	3 (2)	1·00
2 (1)	5 (2)	0·72	1 (<1)	0 (0)	0·50	7 (3)	2 (1)	0·14	2 (1)	1 (1)	1·00
0 (0)	3 (1)	0·25	0 (0)	0 (0)	1·00	1 (<1)	1 (1)	0·61	0 (0)	1 (1)	0·48
4 (1)	3 (1)	0·50	1 (<1)	0 (0)	0·50	0 (0)	2 (1)	0·11	0 (0)	1 (1)	0·48
4 (1)	1 (<1)	0·12	1 (<1)	0 (0)	0·50	2 (1)	0 (0)	0·12	2 (1)	0 (0)	0·50
1 (<1)	0 (0)	0·62	1 (<1)	0 (0)	0·50	0 (0)	1 (1)	1·00	1 (<1)	0 (0)	1·00
1 (<1)	0 (0)	1·00	0 (0)	1 (<1)	1·00	2 (1)	0 (0)	0·25	0 (0)	0 (0)	1·00
8 (3)	3 (1)	0·09	1 (<1)	0 (0)	0·50	8 (4)	9 (5)	1·00	0 (0)	0 (0)	1·00
0 (0)	0 (0)	1·00	0 (0)	1 (<1)	1·00	0 (0)	0 (0)	1·00	0 (0)	0 (0)	1·00
7 (3)	5 (2)	0·58	0 (0)	0 (0)	1·00	8 (4)	2 (1)	0·14	0 (0)	1 (1)	0·48
1 (<1)	0 (0)	0·50	0 (0)	0 (0)	1·00	0 (0)	3 (2)	0·11	0 (0)	0 (0)	1·00
1 (<1)	0 (0)	0·25	1 (<1)	0 (0)	0·50	0 (0)	0 (0)	1·00	1 (<1)	0 (0)	1·00
2 (1)	3 (1)	1·00	1 (<1)	1 (<1)	1·00	4 (2)	4 (2)	1·00	3 (1)	2 (1)	1·00

Table S3. Multivariable analysis of prognostic factors for overall survival and failure-free survival

Overall Survival					
	# of patients	**# of events**	**5yrs OS (95% CI)**	**HR (95% CI)**	**P-value**
Total	660	150			
Treatment group					0.022
Radiotherapy	330	85	76% (71.6-80.9)		
Chemoradiotherapy	330	65	81% (77.2-85.8)	0.68 (0.49 - 0.95)	
Age					<0.001
< 60 years	268	33	89% (85.2-92.8)		
60-69 years	272	73	75% (69.6-80.1)	2.35 (1.54-3.58)	
≥70 years	120	44	65% (57.1-74.5)	3.42 (2.12-5.52)	
Stage					<0.001
Stage I and II	365	66	83% (79.0-86.9)		
Stage III	295	84	74% (68.7-78.9)	2.50 (1.75 - 3.56)	
Histology and grade					<0.001
Endometrioid grade 1 and 2	258	39	86% (82.2-90.7)		
Endometrioid grade 3	213	49	78% (72.9-84.2)	1.91 (1.22 - 2.98)	
Serous / clear cell	189	62	69% (62.4-75.8)	2.57 (1.66 - 3.97)	
LVSI					0.162
No	271	50	83% (78.7-87.9)		
Yes	389	100	76% (71.4-80.1)	1.29 (0.90 - 1.84)	
Lymphadenectomy					0.119
No	281	71	75% (70.5-80.8)		
Yes	379	79	81% (77.3-85.3)	0.74 (0.51 - 1.08)	

* Adjusted for participating groups

Table S3. Multivariable analysis of prognostic factors for overall survival and failure-free survival (continued)

Failure-Free survival					
	# of patients	**# of events**	**5yrs FFS**	**HR (95% CI)**	**P-value**
Total	660	189			
Treatment group					0.007
Radiotherapy	330	105	69% (63.8-73.8)		
Chemoradiotherapy	330	84	76% (71.5-80.7)	0.67 (0.50-0.90)	
Age					<0.001
< 60 years	268	54	81% (75.9-85.4)		
60-69 years	272	89	68% (62.0-73.2)	1.78 (1.26 - 2.52)	
≥70 years	120	46	65% (55.7-72.7)	2.20 (1.45 - 3.32)	
Stage					<0.001
Stage I and II	365	79	79% (74.6-83.1)		
Stage III	295	110	65% (59.0-70.0)	2.62 (1.90-3.60)	
Histology and grade					<0.001
Endometrioid grade 1 and 2	258	61	79% (73.6-83.6)		
Endometrioid grade 3	213	60	73% (66.0-78.1)	1.54 (1.05-2.26)	
Serous / clear cell	189	68	64% (57.1-70.8)	2.12 (1.45-3.10)	
LVSI					0.042
No	271	63	78% (72.8-82.7)		
Yes	389	126	69% (64.1-73.3)	1.38 (1.01-1.89)	
Lymphadenectomy					0.227
No	281	84	72% (65.9-76.6)		
Yes	379	105	74% (68.8-77.8)	0.81 (0.58-1.14)	

* Adjusted for participating groups

Abbreviations: LVSI: lymph vascular space invasion. HR: hazard ratio. CI: confidence interval.

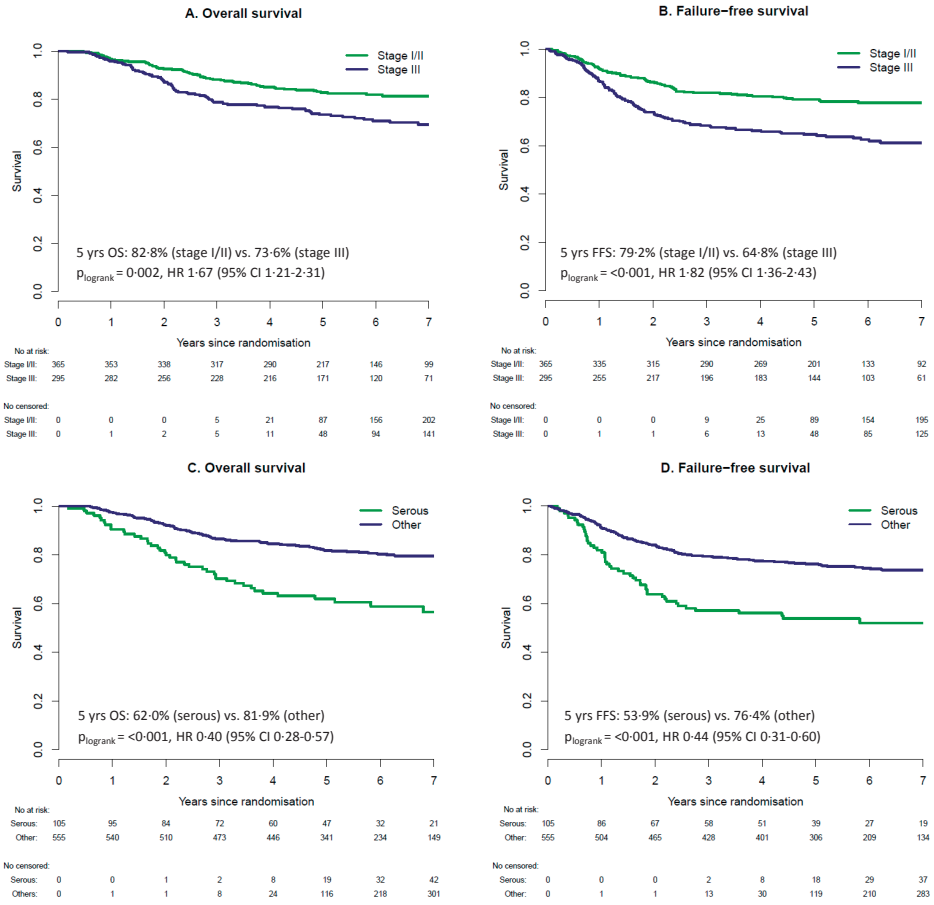


Figure S4. Overall and failure-free survival

Kaplan-Meier survival curve for overall survival (A) and failure free survival (B) in patients with stage I/II versus stage III endometrial cancer. Overall survival and failure-free survival for patients with serous cancer versus all other histological types (C and D).

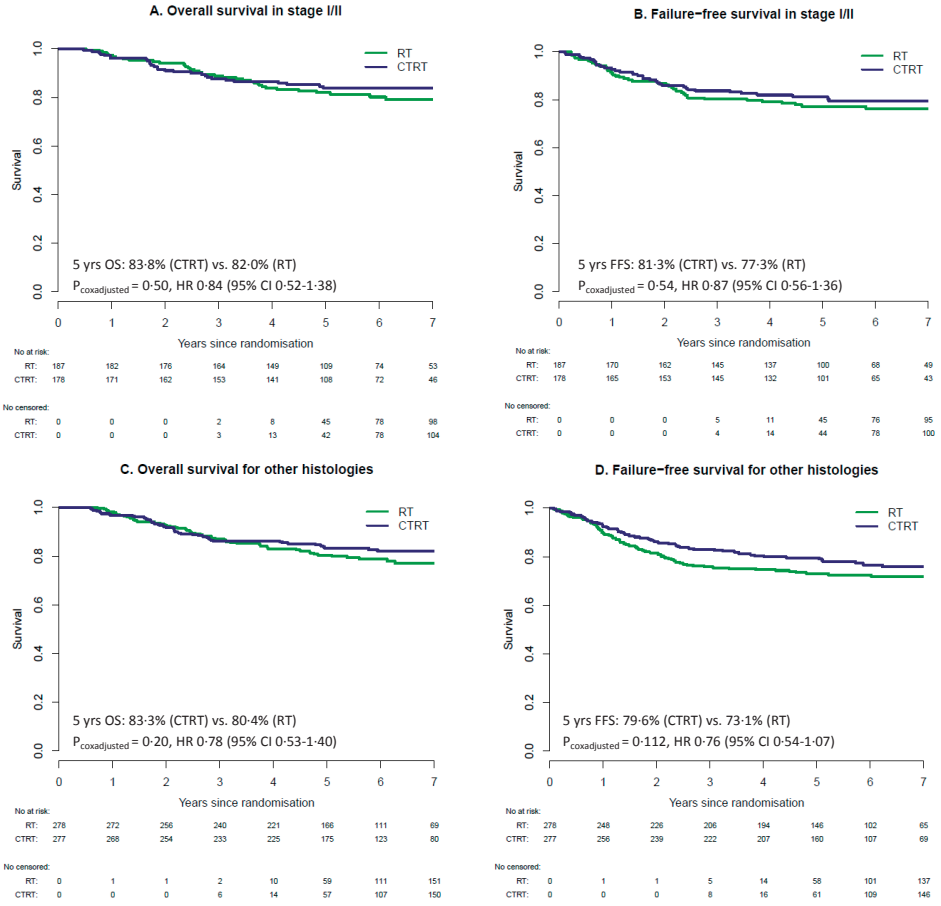


Figure S5. Overall and failure-free survival

Kaplan-Meier survival curve for overall survival (A) and failure free survival (B) in patients with stage I/II endometrial cancer. Overall survival and failure-free survival of patients with a histological type other than serous type (C and D).

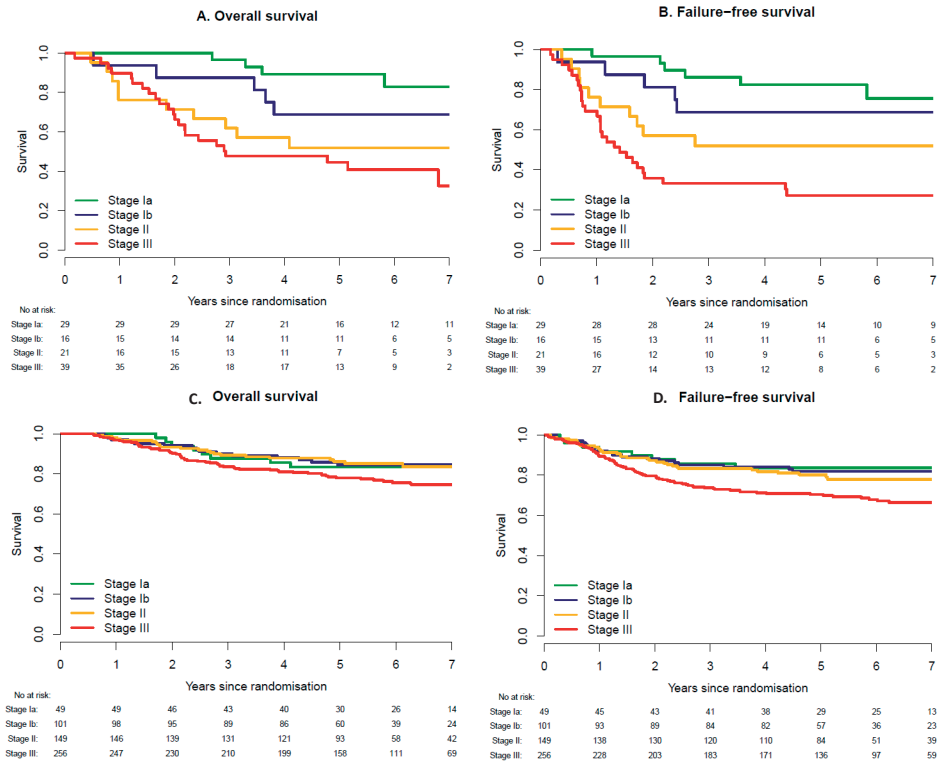


Figure S6. Overall and failure-free survival

Kaplan-Meier survival curves for overall survival (A) and failure free survival (B) in patients with serous endometrial cancer among the different stages; and overall survival (C) and failure-free survival (D) in patients with a histological type other than serous cancer among different stages.

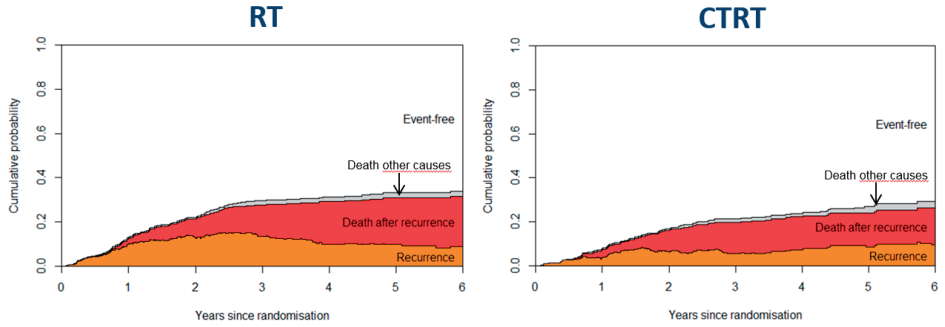


Figure S7. Events and survival by arm

For every time point since randomisation the cumulative probability for a patient was given to be: event-free, alive with an event, deceased after event or deceased due to other causes (intercurrent or second cancer).

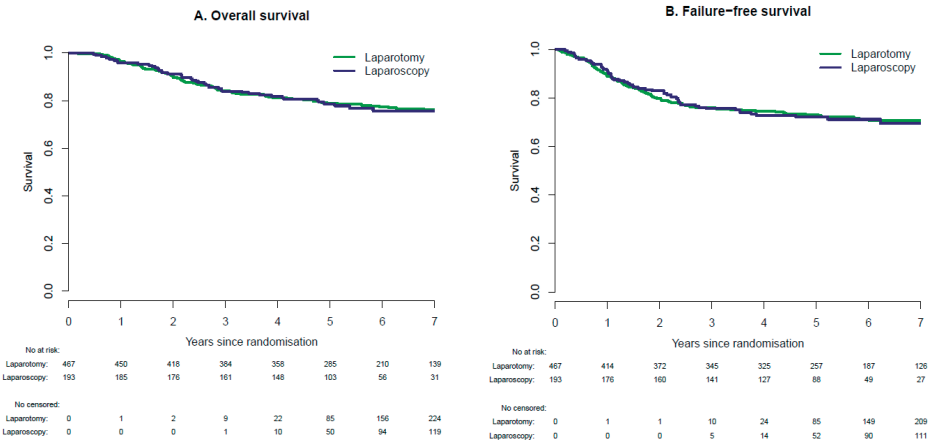


Figure S8. Overall and failure-free survival

Kaplan-Meier survival curve for overall survival (A) and failure free survival (B) in patients who underwent laparotomy compared with patient who underwent laparoscopic surgery

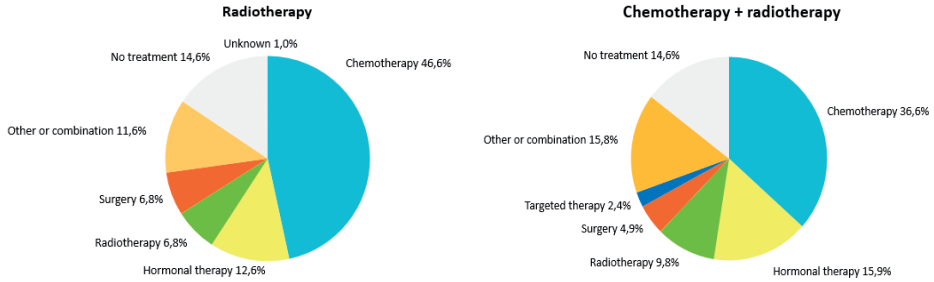
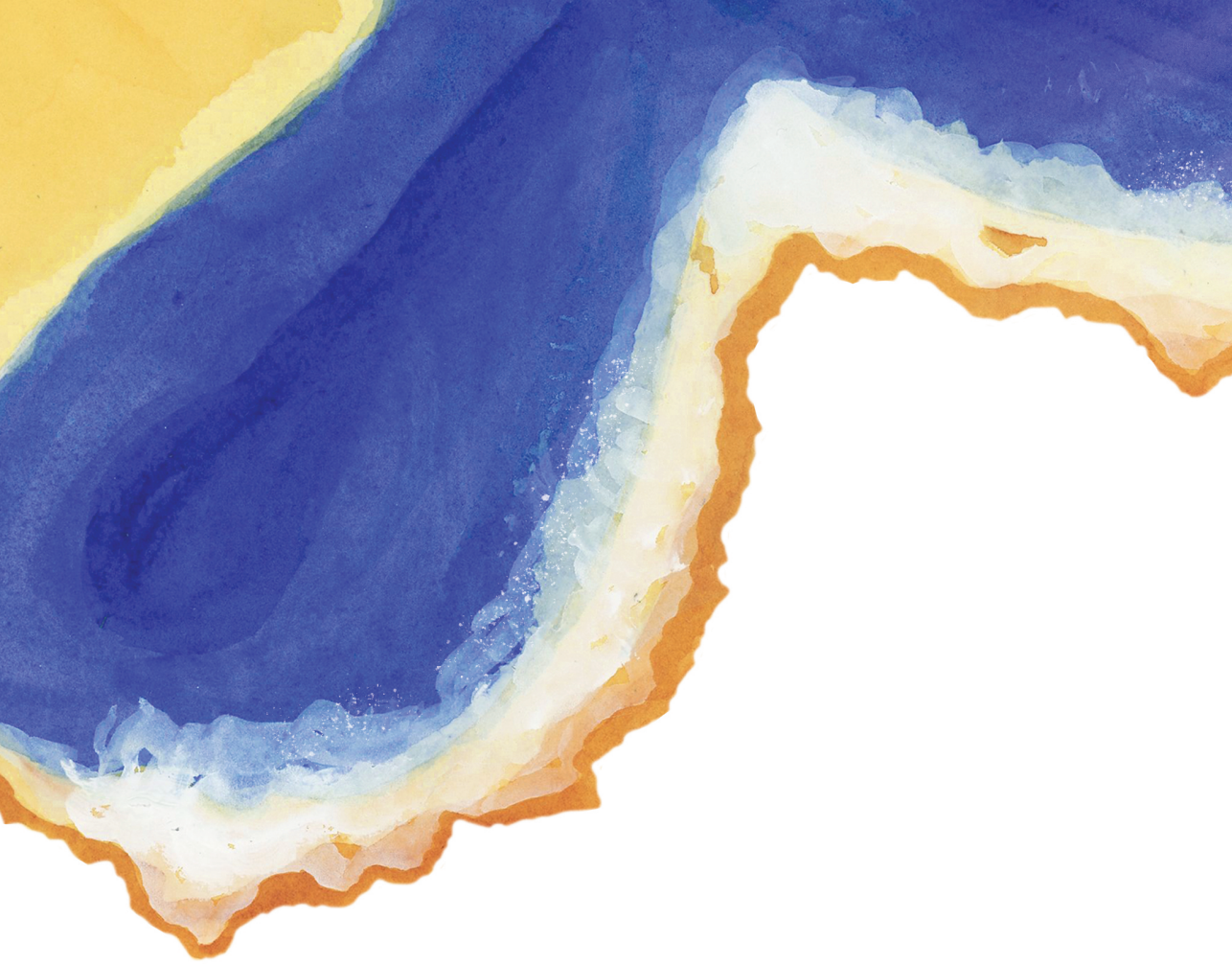
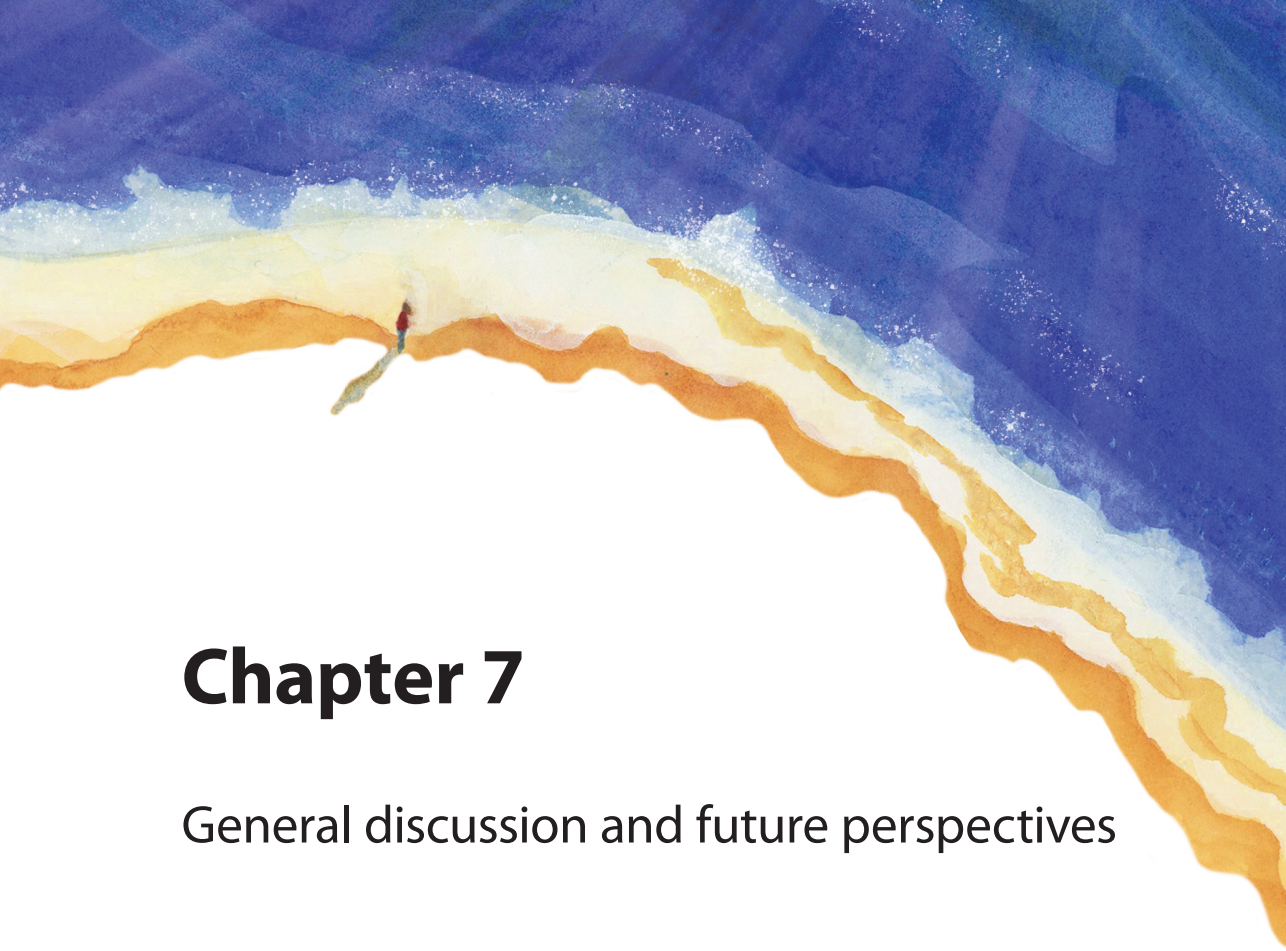


Figure S9. Treatment for first recurrences by treatment arm





Chapter 7

General discussion and future perspectives

7. GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The Post-Operative Radiotherapy in Endometrial Carcinoma (PORTEC) trials are multicentre randomised trials for women with endometrial cancer. In the first PORTEC trial, adjuvant radiotherapy was shown to significantly reduce the risk of locoregional relapse, but without survival difference. It was concluded that radiotherapy should be limited to patients with high-intermediate risk factors, which has led to a substantial reduction of the use of radiotherapy for women with endometrial cancer.[1,2] The second PORTEC trial subsequently showed that vaginal brachytherapy provides similar high vaginal control with less toxicity and better health-related quality of life (HRQOL) compared with external beam radiotherapy.[3,4]

External beam pelvic radiotherapy (EBRT) remained indicated for women with high-risk and advanced stage endometrial cancer to maximize pelvic control. Only approximately 15-20% of women present with high-risk disease at time of diagnosis. As these women are at increased risk of distant metastases and endometrial cancer related death, several trials have been conducted to improve their outcome. Trials comparing adjuvant chemotherapy alone with pelvic EBRT have found no differences in survival (Table 1).[5,6] Because increased pelvic relapse has been reported with adjuvant chemotherapy alone, the combination of EBRT with chemotherapy has been explored in both retrospective and prospective studies.[7-9] In a phase II trial (RTOG 9708) among women with high-risk endometrial cancer, the combination of EBRT with two concurrent cycles of cisplatin, followed by four adjuvant cycles of cisplatin and paclitaxel was tested, resulting in 4-year overall survival of 85%, disease-free survival of 81% and acceptable toxicity profile.

Because the combination of radiotherapy and chemotherapy (chemoradiotherapy) seemed more effective than either treatment alone, and because toxicity and HRQOL data were lacking, the randomised PORTEC-3 trial was initiated. The aim of the PORTEC-3 trial was to evaluate the benefit of chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer in terms of overall and failure-free survival, as well as toxicity and effects on HRQOL. The combined treatment schedule as proven effective in the RTOG phase II trial was used, which has the added advantage of starting both treatment modalities early after surgery. Participating groups were the National Cancer Research Institute (NCRI; UK), Australia and New Zealand Gynaecologic Oncology Group (ANZGOG; Australia and New Zealand), Mario Negri Gynaecologic Oncology Group (MaNGO; Italy), Canadian Cancer Trials Group (CCTG; Canada), and Fedegyn (France).

In this thesis results from the PORTEC-3 trial are presented, as well as the long-term health-related quality of life analysis from the PORTEC-2 trial. In this chapter the main findings of this thesis and their implications are discussed and put into perspective of current literature, focussing on implications for clinical practice and future perspectives.

7.1. Adjuvant treatment for high-risk endometrial cancer

To decide on optimal adjuvant treatment for women with high-risk endometrial cancer, the benefits in terms of survival improvement have to be weighed against the negative aspects such as longer treatment duration and side effects. In the following paragraphs several aspects of adjuvant treatment for high-risk endometrial cancer will be discussed.

7.1.1. Efficacy of adjuvant treatment

In Table 1 an extensive overview of prospective phase III trials investigating adjuvant chemotherapy in high-risk endometrial cancer is presented.[5,6,10-15] Two relatively old trials investigated chemotherapy and/or radiotherapy regimens that would not be used today.[11,12] In the NSGO9501/EORTC55991 trial, EBRT alone was randomly compared with EBRT either preceded or followed by four cycles of platinum-based chemotherapy.[13] Various chemotherapy schedules and sequences were used; the majority of patients (83%) received doxorubicin or epirubicin with cisplatin, but other schedules were allowed. Most patients received radiotherapy before chemotherapy, but 17% received chemotherapy first. The results of this trial were published in a pooled analysis with the unfinished MaNGO ILIADE-III trial, in which women with stage IIB-III endometrioid type EC were randomly allocated to EBRT with or without sequential chemotherapy, given before radiotherapy. Chemotherapy consisted of three cycles of doxorubicin/cisplatin, given every 3 weeks. The pooled analysis of these two trials reported on a total cohort of 534 patients and showed improved progression-free survival (HR 0.63; 95% CI 0.44–0.89; p = 0.009) and a trend for improved overall survival (HR 0.69; 95% CI 0.46–1.03; p = 0.07) with the addition of chemotherapy to EBRT.[13]

The results of the pooled NSGO/EORTC and MaNGO ILIADE-III trial were presented while accrual for the PORTEC-3 was already ongoing, supporting the design of a trial in which an uniform treatment schedule was investigated for high-risk EC women. In the PORTEC-3 trial, 686 patients with high-risk endometrial cancer were randomised to pelvic radiotherapy with or without concurrent and adjuvant chemotherapy. The PORTEC-3 treatment schedule was based on the RTOG 9708 trial[16], with substitution of cisplatin with carboplatin in the adjuvant phase, as this was at the time the established treatment for recurrent or metastatic disease with a more favourable toxicity profile[17].

Overall survival in the PORTEC-3 trial was higher than expected at the time of trial design and as a consequence the required number of overall survival events was not expected to be reached before late 2018 or even 2019. Most recurrences were reported in the first 3 years after treatment and relapse after 5 years was rare. In view of these considerations, the DSMB approved to perform the final analysis as a time-based, rather than an event-based analysis. The final analysis of co-primary endpoints overall survival and failure-free survival as performed in this time-based analysis is presented in **chapter 5**. The overall survival was good (79% at 5 years) considering the high-risk disease

Table 1. prospective phase III trials investigating adjuvant chemotherapy in high-risk endometrial cancer

Trial	Enrolment	No. of patients	Surgery	Eligibility	Randomisation	CT details	OS	RFS	pelvic recurrence
Radiotherapy versus chemotherapy									
Susumu et al (JGOG 2033)[5]	1994-2000	385	TAH-BSO and lymphadenectomy	EEC, stage IC-IIIC, >50% MI	pelvic RT vs CT	3x dyclofosfamide, doxorubicine + cisplatin	5 yrs: 85% vs 87%	5 yrs: 84% vs 82%	5 yrs: 7% vs 7%
Maggi et al(GICOG)[6]	1990-1997	345	TAH-BSO and lymphadenectomy	EEC, stage Ic G3, II G3 (>50%MI), stage III	pelvic RT vs CT	5x dyclofosfamide, doxorubicine + cisplatin	5 yrs: 69% vs 66%	5 yrs: 63% vs 63%	5 yrs: 12% vs 16%
Randall et al (GOG-122)[10]	1992-2000	396	TAH-BSO and lymphadenectomy	Stage III/IV, residual tumor ≤2cm	whole abdominal RT vs CT	8x doxorubicine + cisplatin	5 yrs: 42% vs 55%[#]	5 yrs: 38% vs 50%[#]	5 yrs: 13% vs 18%
Radiotherapy versus chemotherapy + radiotherapy									
Morrow et al (GOG-34)[11]	1977-1986	181	TAH-BSO and lymphadenectomy	Clinical stage I/II (occult), 31% N+	Pelvic RT vs pelvic RT+CT	6-8x doxorubicine	No difference	No difference	NA
Kuoppala et al[12]	1992-1996	156	TAH-BSO and lymphadenectomy	Stage IA–B G3 or IC–IIIA G1–3	Pelvic RT vs pelvic RT+CT	3x cisplatin, epirubicin + cyclophosphamide	No difference	5 yrs: 85% vs 82%	5 yrs: 3% vs 2%
Hogberg et al (NSGO/EORTC)[13]	1996-2007	378	TAH-BSO ± lymphadenectomy	Stage I-III, stage I serous	Pelvic RT vs pelvic RT+CT	Different schedules; 83% doxorubicine + cisplatin	5 yrs: 76% vs 83%	5 yrs: 72% vs 79%[#]	NA
Hogberg et al (MaNGO ILIADE-III)[13]	1998-2007	156	TAH-BSO ± lymphadenectomy	Stage IIB, IIIA-C	Pelvic RT vs pelvic RT+CT	doxorubicin + cisplatin	5 yrs: 73% vs 78%	5 yrs: 61% vs 74%	NA
Pooled analysis[13]		534					5 yrs: 75% vs 82%	5 yrs: 69% vs 78%[#]	5 yrs: 4% vs 2%
de Boer et al (PORTEC-3)	2006-2013	660	TAH-BSO/ TLH-BSO ± lymphadenectomy	Stage I HR*, stage II-III or NEEC stage I-III	Pelvic RT vs pelvic RT+CT	2 x cisplatin concurrent + 4 cycles adjuvant carboplatin + paclitaxel	5 yrs: 77% vs 82%[#]	5 yrs: 69% vs 76%[#]	5 yrs: 1.5% vs 1%

Randall et al (GOG-249)[14]	2009-2013	527	TAH-BSO/ TLH-BSO ± lymphadenectomy	Stage I-II HR*, NEEC stage I-II	Pelvic RT vs VBT+CT	3x carboplatin + paclitaxel	3 yrs: 91% vs 88%	3 yrs: 82% vs 82%	3 yrs: 4% vs 9%[#]
Radiotherapy + chemotherapy versus chemotherapy									
Matei et al (GOG-258)[15]	2009-2014	736	TAH-BSO/ TLH-BSO ± lymphadenectomy	Stage III/IVA* (residual tumor ≤2cm), Stage I+II NEEC	Pelvic RT+CT vs CT	RT+CT: 2 x concurrent cisplatin + 4 cycles adjuvant carboplatin + paclitaxel. CT: 6x carboplatin + paclitaxel	5 yrs: 70% vs 73%	No difference	5 yrs: 10% vs 19%[#]

* FIGO 2009; [#] significant difference ($p<0.05$)

Abbreviations: CT, chemotherapy; RT, radiotherapy; VBT, vaginal brachytherapy; EEC, endometrioid endometrial cancer; NEEC, non-endometrioid endometrial cancer; OS, overall survival; RFS, recurrence free survival; HR, high-risk; G, grade; MI, myometrial invasion; TAH-BSO: total abdominal hysterectomy with bilateral salpingo-oophorectomy; TLH=total laparoscopic hysterectomy. NA, not applicable.

population in this trial, and an improvement of 5% was found for OS in the combined CTRT arm which did not reach statistical significance: 82% in the CTRT arm, vs. 77% in the RT arm; HR 0.76, p = 0.11. A significant 7% improvement of failure-free survival was found for patients in the CTRT arm: 76% vs. 69%, HR 0.71, p = 0.022.

In view of the analysis of the patterns of and survival after recurrence we have updated survival outcomes results with a median follow up of 72 months and with 75% of participating women having reached 5 years of follow up, presented in **chapter 6**. This updated (post-hoc) survival analysis showed statistical significance of the survival improvement with the combination of adjuvant chemotherapy and radiotherapy for high-risk endometrial cancer. The absolute improvements found at 5 years were unchanged, with 5% (HR 0·70, p=0.034) difference for OS and 7% (HR 0·70, p=0.016) for FFS.

The majority of first recurrences were at distant sites, with only few vaginal or pelvic recurrences. Both local and regional control rates were high, reflecting the use of EBRT in both arms. Women in the RT arm more often received chemotherapy for their first recurrence. Median survival after recurrence was 1.4 years and was not significantly different between the two treatment arms.

In the same time period as accrual to PORTEC-3 was ongoing, two randomised trials were running in the United States that investigated adjuvant treatment in high-risk endometrial cancer, the GOG-249 and the GOG-258 trials.[14,15] In the GOG-249 trial, 601 patients with high-intermediate or high-risk stage I-II endometrial cancer were randomised to receive pelvic EBRT alone, or 3 cycles of carboplatin and paclitaxel with vaginal brachytherapy (VBT + CT).[14] Eighty-nine percent had lymphadenectomy and 20% had serous cancer. Final results have been published recently and showed that vaginal brachytherapy with chemotherapy was not superior to EBRT in terms of overall or progression-free survival. Recurrence free survival was 76% in both treatment arms, while overall survival was 87% after EBRT and 85% after vaginal brachytherapy and chemotherapy. However, the number of pelvic recurrences was significantly higher in patients treated with VBT + CT (9% vs 4%), and more frequent and severe acute toxicity was reported in this group. There were no significant differences in PFS by histological type. It was concluded that pelvic EBRT is still the standard of care for women with stage I-II endometrial cancer with high-intermediate or high-risk factors.

To determine the added value of radiotherapy to chemotherapy alone in women with stage III-IVA endometrial cancer, the GOG-258 trial randomly assigned 813 women with stage III-IVA endometrial cancer (97% stage III, 18% with serous cancers) to either pelvic EBRT with concurrent cisplatin and adjuvant carboplatin and paclitaxel (in the same schedule as used in the PORTEC-3 trial), or chemotherapy alone (six cycles of carboplatin and paclitaxel given every 3 weeks).[15] The results were presented at the 2017 ASCO annual meeting and showed overlapping recurrence-free survival (about 60% in both arms) and overall survival curves (73 CT vs 70% CTRT). Significantly more pelvic

and para-aortic lymph node recurrences were reported in patients treated with chemotherapy alone: HR = 0.43 (CI: 0.28–0.66). Women treated with the combined schedule had a trend for more distant recurrence as the first failure (HR = 1.36 (CI: 1.00–1.86). It was not reported how many women with pelvic or para-aortic lymph node recurrence in the chemotherapy-alone arm had salvage radiotherapy.

7.1.2. Adverse events and health-related quality of life

In **chapter 4**, the 2-year adverse events and patient reported health-related quality of life among women treated in the PORTEC-3 trial are presented. Significantly more and more severe acute adverse events (AE) were seen in the combined treatment arm, with grade ≥3 acute AE reported for 60% vs. 12% of patients in the radiotherapy alone arm; these were mainly haematological, GI and bone, joint and muscle-related pain AE. In the first year after randomization the patients recovered well, although 1–3 years after treatment more grade 2 AE were reported for patients treated with CTRT (24 vs. 18% at 3 years, p=0.03), without significant differences in grade ≥3 AE. The only persisting significant difference in grade 2 AE between the two treatment arms was sensory neuropathy, which was reported in 10% vs. 1% after 1 year, in 8% vs. 0% at 3 years and 6% vs 0% at 5 years. The difference in acute adverse events was also reflected in patient-reported health related quality of life (HRQOL). During treatment and in the first 6 months after treatment a decreased HRQOL and lower scores on all EORTC functioning scales were reported. The rapid recovery in the first 6 months after treatment was reflected in the functioning scales as well, and at 1 and 2 years after treatment there were no significant differences, except for a small but significant difference in physical functioning, which is of borderline clinical relevance according to the guidelines of the EORTC QLQ-C30.[18,19] This difference in physical functioning might be related to the increased rate of sensory neuropathy in the combined treatment arm, as 'quite a bit' or 'very much' tingling or numbness was reported by 25% of patients after CTRT compared with 6% after RT at 2 years after treatment. Analysis of long-term adverse events and health-related quality of life of the PORTEC-3 participants is planned.

Data on adverse events (AE) and health-related quality of life (HRQOL) with the addition of chemotherapy to pelvic EBRT in women with endometrial cancer is limited. From first line ovarian cancer trials (MITO-7 and JGOG-3016) with a 3-weekly schedule of carboplatin and paclitaxel (6 cycles) it is known that severe hematological and non-hematological toxic effects, including sensory and motor neuropathy, are common adverse events.[20,21] In Table 2 an overview of acute adverse events in the PORTEC-3, GOG-249 and GOG-258 trials is given, as all trials investigated the combination of chemotherapy and radiotherapy in one of the treatment arms. In the GOG-249 trial more frequent and severe acute AE were reported in the VBT+CT arm (3 cycles of carboplatin-paclitaxel). Overall grade ≥3 acute AE were reported in 64.4% after VBT+CT, in contrast to 11.3% after EBRT. The

vast majority of grade 3-4 AE were of hematological origin. First AE results of GOG-258 reported grade 3-5 hematological toxicity to be the most frequent severe AE (52% for CT versus 40% for CTRT), which is in line with PORTEC-3 in which grade 3-4 hematological toxicity was reported for 45% of women treated with CTRT. In GOG-258 and PORTEC-3 more acute gastrointestinal toxicity was reported for women treated with CTRT: 13% grade 3-5 in GOG 258 and 14% grade 3-4 in PORTEC-3, compared to 6% with RT alone (PORTEC-3) and 4% with chemotherapy alone (GOG-258). Long term adverse events results are awaited for the GOG-249 and GOG-258, but in the PORTEC-3 trial a rapid recovery was seen, with the persistence of grade 2 sensory neuropathy among women treated in the CTRT arm being the most clinically relevant adverse event.

Chemotherapy-induced sensory neuropathy is one of the most bothersome and clinical relevant side effects of treatment. In the ovarian cancer trials (6 cycles of carboplatin-paclitaxel), sensory neuropathy grade 2 and 3 AE were reported in 15% and 2% of patients in the MITO-7 trial, and grade 3 neurologic AE in 7% in the JGOG-3016 trial.[20,21] In the GOG-209 trial for advanced or metastatic endometrial cancer, women treated in one of the treatment arms received 6-7 cycles of carboplatin-paclitaxel and sensory neuropathy grade 2 or higher was reported in 19% of women.[17] In PORTEC-3 and GOG-249, 30% and 9% grade ≥2 sensory neuropathy AE were reported during treatment, with 4 and 3 cycles of carboplatin-paclitaxel, respectively.[14]

The rates of sensory neuropathy AE in the PORTEC-3 trial are somewhat higher as compared with other trials, also in view of the number of cycles. A rapid decline of sensory neuropathy AE in the PORTEC-3 was seen after treatment: at 6 months after randomisation sensory neuropathy grade 2 was reported in 13% and grade 3-4 in 2%; at 12 months this was 9% (grade 2) and 1% (grade 3-4). Despite this rapid decline in sensory neuropathy AE, 25% of women treated in the CTRT arm of the PORTEC-3 reported 'quite a bit' or 'very much' tingling or numbness at 2 years after treatment, reflecting that sensory neuropathy is a long term side effect. Among Dutch ovarian cancer survivors, neuropathy symptoms were experienced by 51% of women who received chemotherapy even up to 12 years after treatment. A higher neuropathy score was associated with more cycles of chemotherapy, more recurrences and a shorter period since treatment. The sensory neuropathy clearly affected their health-related quality of life, with lower levels of functioning and overall quality of life and more symptoms such as fatigue.[22]

Long term health-related quality of life (HRQOL) in the PORTEC-2 trial is presented in **chapter 2**. This analysis shows that EBRT may have a long-lasting, clinically relevant, mostly bowel symptom related negative impact on HRQOL, with moderate or severe limitation of daily activities reported by 10% of the patients. After treatment with EBRT, women reported significantly more diarrhea, fecal leakage, urgency, and limitations in daily activities due to bowel symptoms, as well as a trend for more urinary symptoms

Table 2. Overview of acute adverse events in prospective phase III trials investigating the combination of chemotherapy and radiotherapy in one of the two treatment arms

	de Boer et al (PORTEC-3)	Randall et al (GOG-249)[14]	Matei et al (GOG-258)[15]
	CTRT vs RT	VBT + CT vs RT	CTRT vs CT
Overall highest grade 2	34% vs 31%	28% vs 35%	NA
Overall highest grade 3	46% vs 13%	31% vs 11%	NA
Overall highest grade 4	15% vs 0%	33% vs 1%	NA
Hematological grade 3-4	45% vs 6%	Leukocytes: 30% vs 0%; neutrophils: 58% vs 0%	40% vs 52%
Gastro-intestinal (any) grade 3-4	14% vs 6%	4% vs 3%	13% vs 4%
Diarrhea grade 3-4	11% vs 4%	2% vs 3%	NA
Nausea grade 3-4	3% vs 1%	1% vs 0%	NA
Alopecia grade 2	57% vs <1%	48% vs <1%	NA
Fatigue grade 2	21% vs 2%	21% vs 9%	81% vs 78% (grade 1-2)
Pain (any) grade 2	31% vs 7%	24% vs 4%	62% vs 63% (grade 1-2)
Pain (any) grade 3-4	9% vs 1%	4% 1%	8% vs 5%
Sensory neuropathy grade 2	23% vs 0%	7% vs 1%	Neurology: 74% vs 69% (grade 1-2)
Sensory neuropathy grade 3-4	7% vs 0%	2% vs 0%	Neurology: 7% vs 5%

Abbreviations: CT, chemotherapy; RT, radiotherapy; VBT, vaginal brachytherapy; TAH-BSO: total abdominal hysterectomy with bilateral salpingo-oophorectomy; TLH=total laparoscopic hysterectomy. NA, not applicable.

compared with women treated with vaginal brachytherapy (VBT). This increase in symptoms did not lead to a significant differences in general health and overall quality of life, or to differences in other cancer survivorship issues. These results are in line with rates of gastrointestinal and bladder toxicity found in other studies.[23,24] Similar to long-term HRQOL findings in the PORTEC-1 trial, there was a trend for more urinary symptoms for women treated with EBRT 7 years after randomization, with moderate or severe symptoms for urinary urgency in 39% (EBRT) vs 25% (VBT); a difference that was not seen in the 5-year HRQOL analysis. Longitudinal analysis showed increasing rates of urinary frequency over time in both groups but more so among EBRT patients, showing the combined effects of ageing and EBRT on the bladder and pelvic floor. Pelvic floor dysfunction is a common problem among older women but is even more pronounced among gynaecologic cancer survivors.[25,26] Pelvic floor muscle training programs in small studies suggested improved results compared with usual care.[27,28]

When comparing the health related quality of life among women treated in the EBRT arm of the PORTEC-2 and PORTEC-3 trials there is a similar pattern of both functioning scales and symptoms during treatment and in the first two years thereafter. During

treatment and in the first 6 months after treatment completion, an increase of symptoms was reported by patients, with a gradual decrease thereafter. Global health, physical and role functioning were lower at baseline (after surgery) and during follow-up until 2 years after randomization among women treated in the PORTEC-2 trial compared with those treated in the PORTEC-3 trial.[4,29] A possible explanation for this difference could be the higher median age of PORTEC-2 (70 years) compared to PORTEC-3 participants (62 years). Furthermore, improvements in radiation techniques have showed to reduce gastro-intestinal and genito-urinary toxicity for the treatment of gynecological cancers (discussed in paragraph 7.3.2.).[30-32]

7.1.3. Upfront pathology review

Adjuvant treatment for endometrial cancer is based on a combination of pathology and clinical criteria. It is therefore important that the reproducibility of pathology diagnosis is good. Previous studies reported high rates of interobserver variability for pathological assessment of gynecological tumours.[33-35]

In the PORTEC-3 trial, upfront pathology review was done to include only truly high-risk patients in the trial. Analysis of pathology review in the Netherlands and the United Kingdom (48% of PORTEC-3 participants) showed that central pathology review by expert gynaeco-pathologists changed histological type, grade or other items in 43% of women with high-risk endometrial cancer (**chapter 3**). Highest rates of disagreement between observers have been reported for histological grade and type. Previous studies have shown that binary grading assessing high grade versus low grade should be preferred, as the reproducibility of grade 2 is limited.[36-38] For assessment of histological type, interobserver agreement rates varying from 62-83% have been reported in several studies for high-risk endometrial cancer.[39-41] A previous study has shown that consensus can be increased by the use of immunohistochemical (IHC) markers. With a panel of three IHC markers (P53, ER and CDKN2A) consensus was reached in 96% of cases, compared with 72% without the use of IHC.[39] The use of IHC was not routine practice in the period of the PORTEC-3 trial and was only performed incidentally.

Both at pathology review in the Netherlands and the United Kingdom, changes in pathology items led to ineligibility for the PORTEC-3 trial in 8% of cases, most frequently due to differences in the assessment of histological type, endocervical stromal involvement and histological grade (**chapter 3**). These patients did not enter the trial and this prevented lower-risk patients from receiving unnecessary toxic treatment. The percentage of cases deemed ineligible at pathology review was considerably lower than at pathology review in the PORTEC-1 and 2 trials, where 24% and 14% of women, respectively were in retrospect ineligible. Eligibility in these two trials was determined by a combination of grade, myometrial invasion and histological type, and differences in eligibility were often caused by a shift from grade 2 to grade 1. Such a grade shift did not

affect the PORTEC-3 trial where patients had to have either grade 3 or non-endometrioid histology or more advanced stages.

Besides preventing unnecessary toxic treatment, the upfront pathology review resulted in a true high-risk endometrial cancer trial population and reliable pathology assessment, which ensures the quality of future translational research. In view of these advantages, upfront pathology review is to be preferred in future gynecological oncology trials. In daily clinical practice pathology review is recommended as well, as it can avoid over-and undertreatment, especially when treatment modalities with substantial toxicity are considered.

Challenges for upfront pathology review are that review is time-consuming and expensive. Further standardization of pathology criteria and subspecialisation in gynaecopathology are therefore essential. Rapid access to expert consultation is important which will be facilitated by the transition to digital pathology. Finally, the introduction of immunohistochemistry and molecular analysis using the Cancer Genome Atlas Group (TCGA) molecular subgroup classification (discussed in paragraph 7.2.3.) will further improve risk assignment.[42,43]

7.2. Current issues in adjuvant treatment for high-risk endometrial cancer

7.2.1. Which patients benefit from chemotherapy?

High-risk endometrial cancer is a heterogeneous group of tumours, comprising both early-stage endometrial cancer with high-risk tumour characteristics, as well as more advanced stages endometrial cancer and non-endometrioid tumours. Both the NSGO/EORTC and the PORTEC-3 trials have reported a significant benefit in terms of recurrence-free survival with the addition of chemotherapy to radiotherapy, and a significant improvement in overall survival was reported in the PORTEC-3 trial.[13] In **chapter 6**, subgroup analyses by stage and histological type are provided.

Dividing this group of high-risk endometrial cancer patients by stage, women with stage III endometrial cancer had a significant higher risk of recurrence compared with women with stage I-II endometrial cancer (5-year failure free survival 65% versus 79%). Two trials, the GOG-249 [14] and the PORTEC-3 trial reported a good local control for stage I-II high-risk endometrial cancer after EBRT alone. In the subgroup analysis for stage I-II in the PORTEC-3 trial, a non-significant benefit of 2% for OS and 4% for FFS at 5 years was found with the addition of chemotherapy to radiotherapy. For this group of patients, the potential benefit of chemotherapy seems too limited to justify the increase in adverse events and impaired quality of life and longer treatment duration for these patients.

For women with stage III endometrial cancer, a significant and clinically relevant benefit of 10% in overall survival and 12.5% in failure free survival was found in favour of the combination of chemotherapy and radiotherapy in the PORTEC-3 trial. In the GOG-258 trial, more vaginal, pelvic and para-aortal recurrences were reported in patients with

stage III/IV disease with chemotherapy alone, while there was no difference in progression-free and overall survival compared with combined CTRT.[15] Taking these results together, combined adjuvant chemotherapy and radiotherapy should be discussed and recommended for women with stage III endometrial cancer to optimize failure free and overall survival as part of shared decision making.

In the PORTEC-3 trial, women with serous cancers, including mixed histologies with at least 25% serous component, had significant lower overall and failure-free survival compared with women with endometrioid or clear cell cancers. Both overall and failure-free survival were significantly improved for serous cancers by the addition of chemotherapy to radiotherapy; 5 year overall survival was 71% (CTRT) vs 53% (RT) and 5-year failure-free survival was 60% (CTRT) vs 48% (RT), with a HR of 0.48 for OS and 0.42 for FFS. Several study groups have performed subgroup analyses to determine the interaction between histology and treatment. In retrospective series OS and RFS benefits have been reported with chemotherapy for serous cancers.[44,45] In the combined analysis of the NSGO/EORTC and MaNGO ILIADE-III trials, a significant effect on both failure-free and overall survival was found with the addition of chemotherapy for endometrioid tumours, while no effect was found for serous cancers.[13] In other randomised trials however, subgroup analyses revealed no difference in treatment effect among different histological types. The GOG evaluated the relation between histology and outcome in 1203 patients with advanced and metastatic endometrial cancer participating in first-line chemotherapy trials; no differences in effect of treatment was found for the various histological types.[46]

These subgroup analyses should be interpreted with caution as the number of serous cancers in all of these trials was relatively limited. Serous cancers have been grouped together with clear cell cancers in most of these trials, while the rates of recurrence for clear cell cancers in the PORTEC-3 trial was comparable to endometrioid tumours and clearly lower than for serous cancers. It is also important to note that different chemotherapy agents have been used in the various trials. In most of these trials platinum-based chemotherapy schedules were used and only few patients received a taxane-based chemotherapy schedule, while in PORTEC-3 all patients in the CTRT arm were treated with platinum- and taxane-based chemotherapy. This may have improved efficacy for serous cancers.

7.2.2. Is the PORTEC-3 schedule the best schedule of radiotherapy and chemotherapy?

One of the strengths of the PORTEC-3 trial is that a uniform treatment schedule has been used, something that was lacking in older trials. The question is whether this is the best schedule. The PORTEC-3 trial was based on the RTOG-9708 phase 2 trial[16], with substitution of cisplatin by carboplatin for the adjuvant cycles to reduce toxicity and in view of the standard use of carboplatin–paclitaxel in metastatic or recurrent disease.[17] To start both radiotherapy and concurrent cisplatin early after surgery, we aimed for rapid

efficacy of both modalities and for a potential increase of radiotherapy effect by the two concurrent cycles. Internationally, there is a widespread difference in the sequence of giving chemotherapy and radiotherapy. The combined schedule is time efficient and has now been proven safe and effective in two large, randomised trials (PORTEC-3 and GOG-258) with toxicity and health-related quality of life data. There is no phase III evidence of specific benefit for other sequences of radiotherapy and chemotherapy. Most first recurrences were at distant sites so one could speculate whether 4 or 6 cycles of adjuvant carboplatin-paclitaxel should be given. In the GOG-258 trial, a trend but no significant improvement for recurrence at distant sites was reported for women treated with 6 cycles of chemotherapy.

7.2.3. Integration of molecular characteristics in the risk classification

In 2013, the Cancer Genome Atlas Group (TCGA) provided a molecular classification of endometrial cancer with four subclasses based on mutational burden and copy number alterations, with clear prognostic implications (Figure 1).[47] The first subclass of ultramutated tumours is characterized by mutations in the exonuclease domain of DNA polymerase epsilon (*POLE*), and although associated with a high tumour grade, these have a very good prognosis.[48] The second subclass consists of hypermutated microsatellite-unstable tumours, which is caused by mismatch-repair (MMR) deficiency. Most often the MMR-deficiency is caused by MLH1 promotor hypermethylation, but in a small subset of cases this is due to a germline mutation in one of the MMR-genes (Lynch syndrome). The third subclass is characterized by high somatic copy number alterations, is driven by *TP53* mutations, and consists of high-grade (mostly serous) cancers; for this group the poorest prognosis has been reported. The fourth subclass is the copy number low group which is characterized by a low mutational burden and contains most endometrioid endometrial cancers; this group does not have a specific molecular profile.[47]

These molecular subclasses have been determined by whole genome sequencing on fresh tumour tissues. Several groups have shown that the molecular groups can also be reliably determined in formalin fixed, paraffin embedded tissues by their surrogate markers, with equally strong prognostic impact (Figure 2A and 2B).[42,43,49,50]

Translational analysis in the PORTEC 1 and 2 trial cohorts integrated the molecular subgroups proposed by the TCGA with results of a multigene mutation analysis, other established biomarkers and clinicopathological risk factors. The inclusion of L1CAM, *CTNNB1* and lymph vascular space invasion (LVSI) in addition to the TCGA subgroups showed an improved risk assessment in the PORTEC 1 and 2 trial cohorts.[42] In this molecular integrated risk model, stage I endometrial cancers at (high) intermediate risk could be reclassified to favorable (50%), intermediate (35%) or unfavorable risk groups (15%).

This integrated risk assessment is now being prospectively tested in the PORTEC-4a trial.[51,52] In this trial, a molecular integrated risk assessment is used to define adjuvant treatment (Figure 3a). In this trial, patients with stage I, high-intermediate risk endometrial cancer are randomised (1:2) to standard adjuvant vaginal brachytherapy or to the experimental arm in which adjuvant treatment is based on the integrated molecular profile. In this arm, patients are divided into three subgroups based on the profile, which is based on determination of the TGCA groups, L1CAM expression, LVSI, and *CTNNB1* mutation (Figure 3b). The favourable subgroup of otherwise high-intermediate risk endometrial cancer (approximately 55%) will receive no adjuvant treatment. The intermediate subgroup (~40%) will receive vaginal brachytherapy. Patients with an unfavourable profile (~5%) will be treated with external beam radiotherapy. The primary end point is vaginal recurrence; secondary end points are pelvic and distant recurrence, overall and recurrence-free survival, quality of life and health care costs. First results of the pilot phase of the PORTEC-4a showed a feasible trial concept with a satisfactory patient acceptance rate and optimized workflow of the determination of the molecular-integrated risk profile.[53]

Data regarding the use of molecular classifiers for women with high-risk, non-endometrioid (serous, clear cell) tumours or women with more advanced stage of disease are limited. In an international cohort of 381 endometrioid grade 3 tumours, molecular analysis revealed a mixture of molecular subtypes of endometrial cancer, each with their own prognosis (Figure 2c).[54] To explore whether the risk assessment of high-risk endometrial cancers can be refined using TGCA molecular subgroups, the TransPORTEC consortium evaluated 116 high-risk endometrial cancer patients and reported that molecular analysis can discriminate between patients with a favourable and intermediate prognosis (*POLE*-mutant or microsatellite instability, respectively) and those with less favourable outcomes (no specific molecular profile) or unfavourable prognosis (p53 mutant expression).[55] To determine the molecular characteristics in a large trial cohort with high-risk endometrial cancer patients, translational research within the transPORTEC consortium is being performed on tumour tissue blocks donated by over 400 PORTEC-3 patients. The molecular subgroups as described by the Cancer Genome Atlas Group are determined.[47] Molecular subclass specific benefits of combined chemotherapy and radiotherapy will be explored together with assessment of other characteristics and targets such as DNA repair damage, genome scarring, immunological reactivity, and *TP53* pathway abnormalities. First results are expected late 2019.

7.3 Future perspectives

7.3.1. Implementation of molecular characteristics into the clinic

Due to the heterogeneity of high-risk endometrial cancer, it is likely that the benefit of chemotherapy is more pronounced in a subgroup of patients. An important future chal-

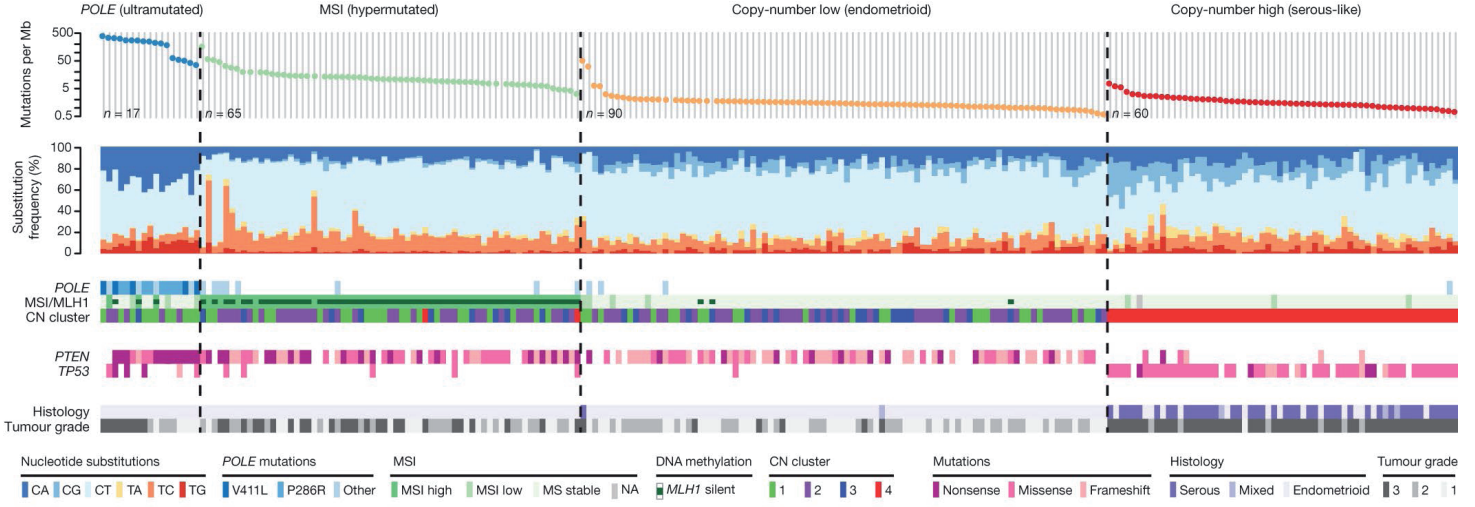


Figure 1. Molecular characterization of endometrial cancer proposed by the Cancer Genome Atlas Group[47]

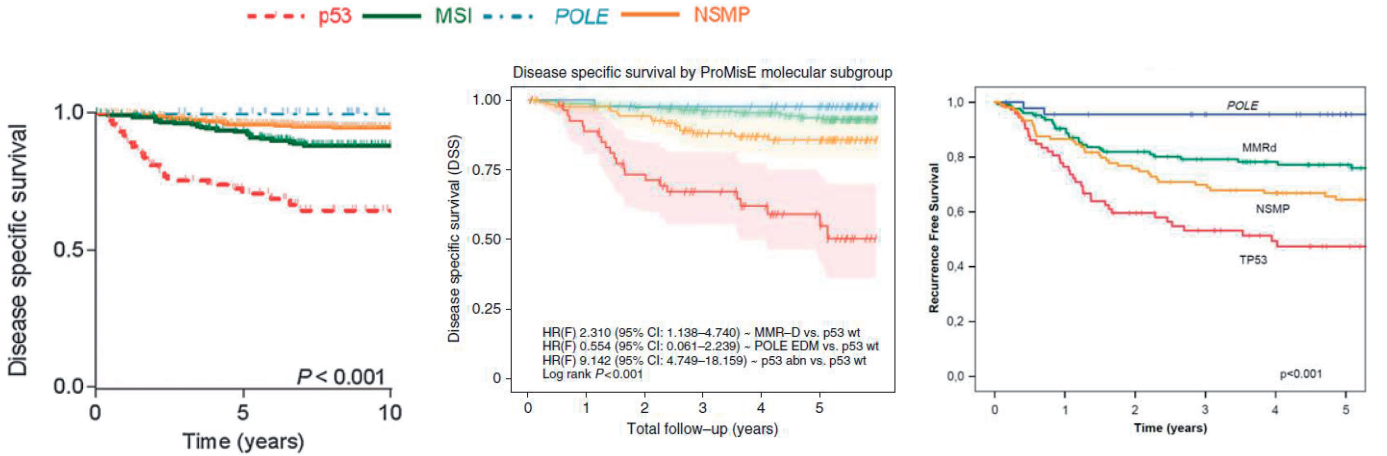


Figure 2. Prognostic significance of the TCGA subgroups in: (A) low-intermediate risk endometrial cancer in the PORTEC 1 and 2 trial[42]; (B) in an unselected retrospective German cohort (validation cohort of ProMisE)[50] and in (C) an international cohort of endometrioid grade 3 tumours.[54]

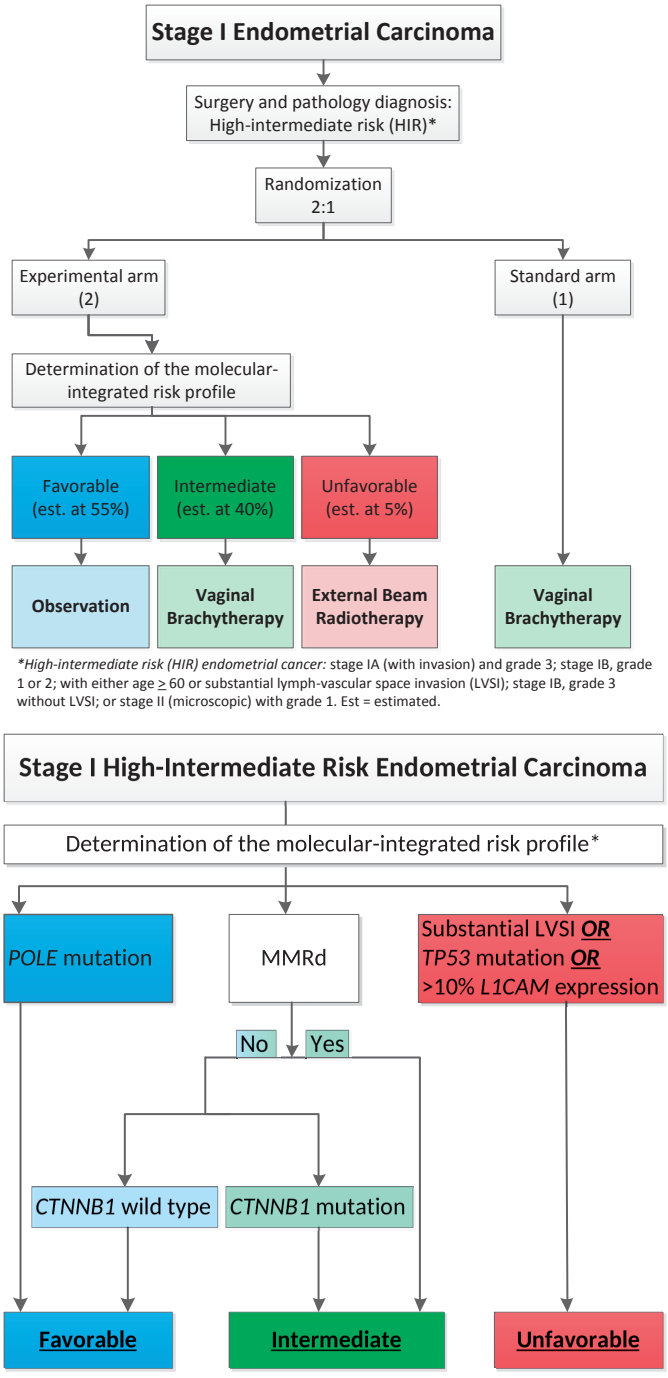


Figure 3. PORTEC-4A trial design (A) and decision tree of the molecular-integrated risk profile (B).[53]

lenge is to better select the patients who benefit most from chemotherapy, to reduce under- and overtreatment. A molecular integrated risk model (as being explored in the PORTEC-4A trial) has the potential to select women who will have benefit of the addition of chemotherapy to radiotherapy, while for others specific targeted treatments may be preferable.

Molecular analysis might be used in the preoperative setting to decide on the optimal surgical approach, as two studies reported good concordance in molecular alterations and classifications on diagnostic endometrial samples and final hysterectomy specimens.[56,57] Depending on the molecular characteristics the extent of surgery could be decided in future studies.

The PORTEC-4A trial is the first trial that uses a molecular integrated risk assessment to define adjuvant treatment. Future (prospective) studies should address the role of the molecular integrated risk classifiers to direct both adjuvant and definitive treatment of specific subgroups of high-risk endometrial cancer, and to identify molecular alterations sensitive to tailored targeted therapies. In *POLE* mutant and MSI/MMRd tumours, high numbers of tumour-infiltrating CD*8 T-cells and higher densities of PD-1 and PD-L1 expressing immune cells have been found compared to NSMP and p53 mutant tumours.[58,59] It was suggested that especially MSI tumours are attractive candidates for checkpoint inhibition, as the antitumour immune response can be enhanced by immune checkpoint inhibition. This was also suggested for *POLE* mutant tumours although these tumours already have a good prognosis. First small studies of checkpoint inhibitors for advanced stage and/or recurrent *POLE* and MMRD endometrial cancers have indeed shown promising results[60-63].

A potential targeted therapy which is being investigated is poly-(ADP-ribose)-polymerase-enzymes (PARP)-inhibition. PARP inhibition has been proven effective in women with ovarian cancer, especially among women with homologous recombination deficiency (HRd), which impairs the repair of double strand DNA breaks.[64] Recently a small first study has reported that HRd is frequent in high-grade endometrial cancer, especially among non-endometrioid, *TP53*-mutant tumours.[65] A phase II trial of the combination of checkpoint inhibition and PARP inhibition in advanced and metastatic endometrial cancer (DOMEC), initiated by the Dutch Gynaecological Oncology Group (DGOG) will start accrual in 2019 (NCT03951415). The hypothesis of this trial is that the combination of PD-L1 and PARP inhibition has a synergistic effect and will result in an improved progression free survival. For *TP53*-mutant tumours, overexpression of human epidermal growth factor receptor 2 (HER2/Neu) has been reported in 25% of cases, with potential benefit of adding trastuzumab to chemotherapy.[47,66] For NSMP tumours the molecular landscape needs to be further investigated to define molecular alterations that can be used to refine the risk of recurrence and to explore potential targets for therapy.

7.3.2. Improvement of radiation techniques

Improvements in radiation techniques have been shown to reduce doses to the surrounding organs, leading to reduced gastro-intestinal and genito-urinary toxicities in the treatment of gynecological cancers. Compared to parallel opposing fields or four-field techniques, intensity-modulated radiation therapy (IMRT) reduced the dose delivered to normal tissues, with the use of multiple beams or arcs. In a randomised trial (NRG Oncology/ RTOG 1203), the TIME-C trial, women with cervical or endometrial cancer were randomly assigned to standard four-field or IMRT techniques. Women treated with IMRT reported significantly less gastro-intestinal and urinary toxicity than women treated with standard four-field radiotherapy (Figure 4).[30]

Currently, the majority of women treated with radiotherapy in the Netherlands are being treated with volumetric arc therapy (VMAT). VMAT delivers radiotherapy while the gantry rotates around the patient, using a multi-leaf collimator which dynamically alters the shape of the treatment field, with variable dose rates and gantry speed.[67] This leads to a decreased number of monitor units and a shorter overall treatment time per fraction compared to IMRT. For gynecological cancers, the majority of data for VMAT is limited to planning studies.[68-70] Although lower doses to the bowel and bladder have been reported, quality of life data are very limited. Based on the results of the TIME-C trial which showed significantly less gastro-intestinal and urinary toxicity with IMRT, toxicity with VMAT might even be lower compared to IMRT. Further reductions in the dose to the surrounding organs might be achieved by the use of proton therapy. Studies have reported that the advantage of proton therapy is mainly observed in lower dose regions, especially for bowel, kidneys and bone.[71,72] The greatest clinically relevant advantage of proton therapy was found for treatment of macroscopic disease in the para-aortic region. In the APROVE study 25 women with endometrial or cervical cancer will receive adjuvant pelvic radiotherapy with proton therapy to evaluate safety and treatment tolerability. Secondary endpoints include toxicity and quality of life analysis.[73] Future studies are necessary to evaluate the acute and long term side effects and the impact on quality of life.

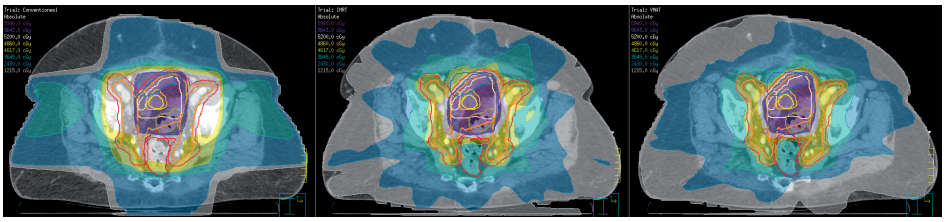


Figure 4. Examples of dose distributions of pelvic external beam radiotherapy for three different radiation techniques (A) 3-dimensional conformal radiotherapy, (B) intensity modulated radiotherapy and (C) volumetric modulated arc therapy.

Isodose lines: purple 5940 cGy; slateblue 5643 cGy; white 5200 cGy; yellow 4860 cGy; yellowgreen 4617 cGy; teal 3645 cGy; steelblue 2430 cGy; grey 1215 cGy

7.4. Shared decision making

Endometrial cancer primarily affects older women, and the median age of patients with high-risk disease is even higher. However, women with high-risk endometrial cancer are at increased risk of distant metastases and endometrial cancer related death. It is therefore important to weigh the benefits in terms of survival benefit against the costs in terms of toxicity, treatment duration and both short-term and long-term health-related quality of life. Although the PORTEC-3 trial showed improvement in overall and failure free survival, the addition of chemotherapy to radiotherapy is leading to increased toxicity and lower quality of life during treatment and the first year thereafter. The persistence of sensory neuropathy among women treated with chemotherapy is the most clinically relevant and most bothersome symptom. It is therefore important to involve the patient in shared decision making and to provide comprehensive information. In a patient preference study done by the ANZGOG group among PORTEC-3 participants prior to randomisation, the minimum survival benefit to make adjuvant chemotherapy worthwhile was 5% or an extra 1 year for more than 50% of patients.[74] Over 50% of clinicians judged an extra 1 year of survival time or an extra 10% survival benefit sufficient to justify chemotherapy. The reported benefit in progression-free survival and overall survival found in the recent trials is within this range, especially for those with stage III and/or serous disease. However, patients' preferences varied over a wide range. Therefore, individual patient counselling and shared decision-making remain essential.

7.5. Conclusion

The majority of women with endometrial cancer present with early-stage disease and have a favourable prognosis. About 15-20% of women with endometrial cancer are diagnosed with higher risk disease, and these women have an increased risk of distant metastases and endometrial cancer related death. An improved risk stratification will help us to identify those women who have truly high risk disease. The ultimate goal is to improve outcome for women with high-risk endometrial cancer with as little treatment-related toxicity as possible. The PORTEC-3 trial has been essential in providing evidence that the addition of chemotherapy to radiotherapy improved overall and failure free survival for women with high-risk endometrial cancer. Unfortunately, this comes at the expense of increased adverse events and a (transient) impairment of the patients' quality of life. For both clinicians and patients the trade-off between estimated risk of recurrence and likely toxicities is difficult. The potential benefit is limited to a subset of patients, while toxicities are relatively frequent. It is essential that we select those women who will have most benefit of the addition of chemotherapy.

Molecular analysis has the potential to improve risk stratification and identify true high-risk patients, and to direct adjuvant treatment. To bring these molecular risk factors into the clinic, strong international collaboration is needed as specific subgroups are small,

and studies for both primary and recurrent disease are needed. Although there are still many unanswered questions, the integration of molecular risk factors has the potential to lead to significant changes in standard practice in the near future.

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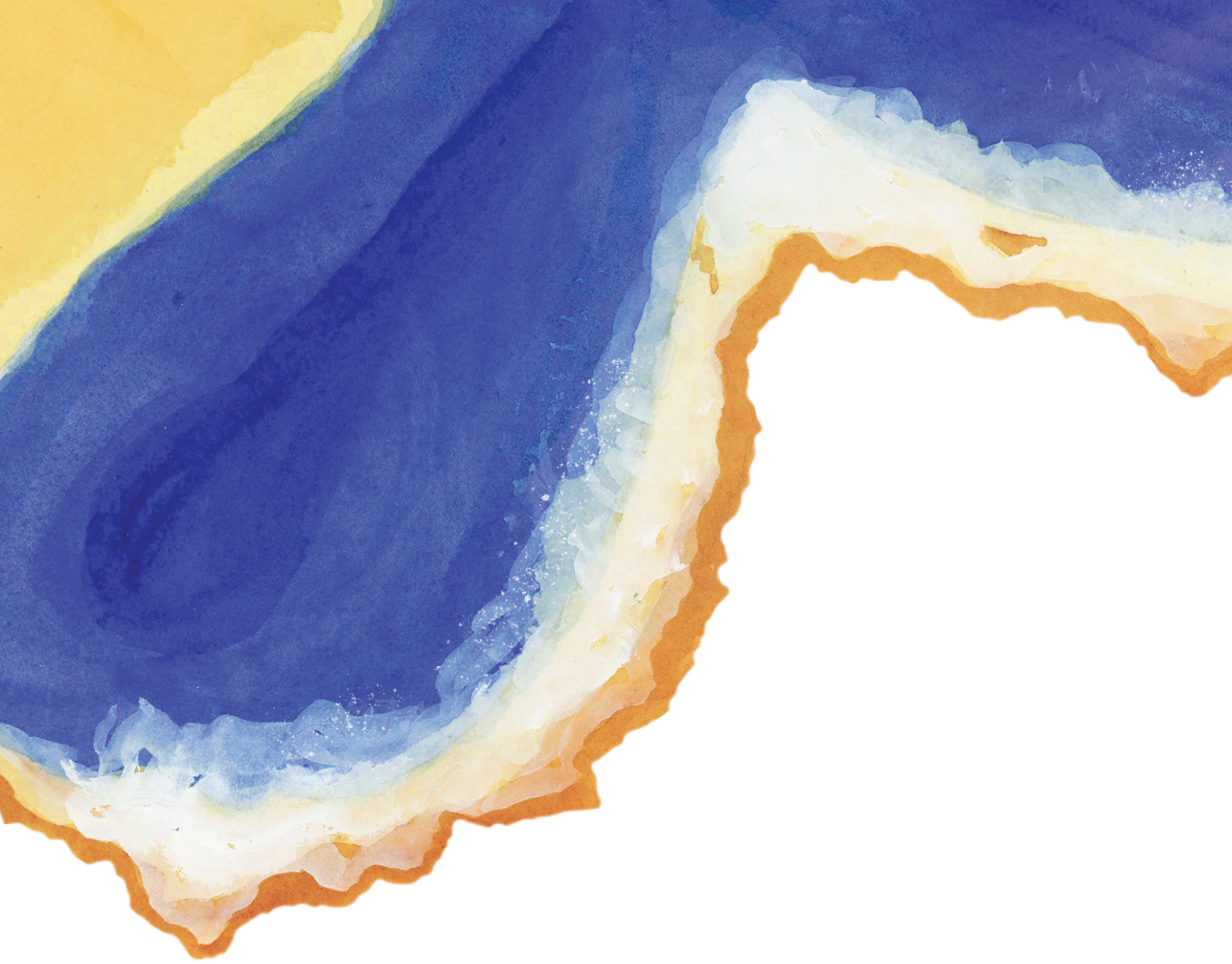

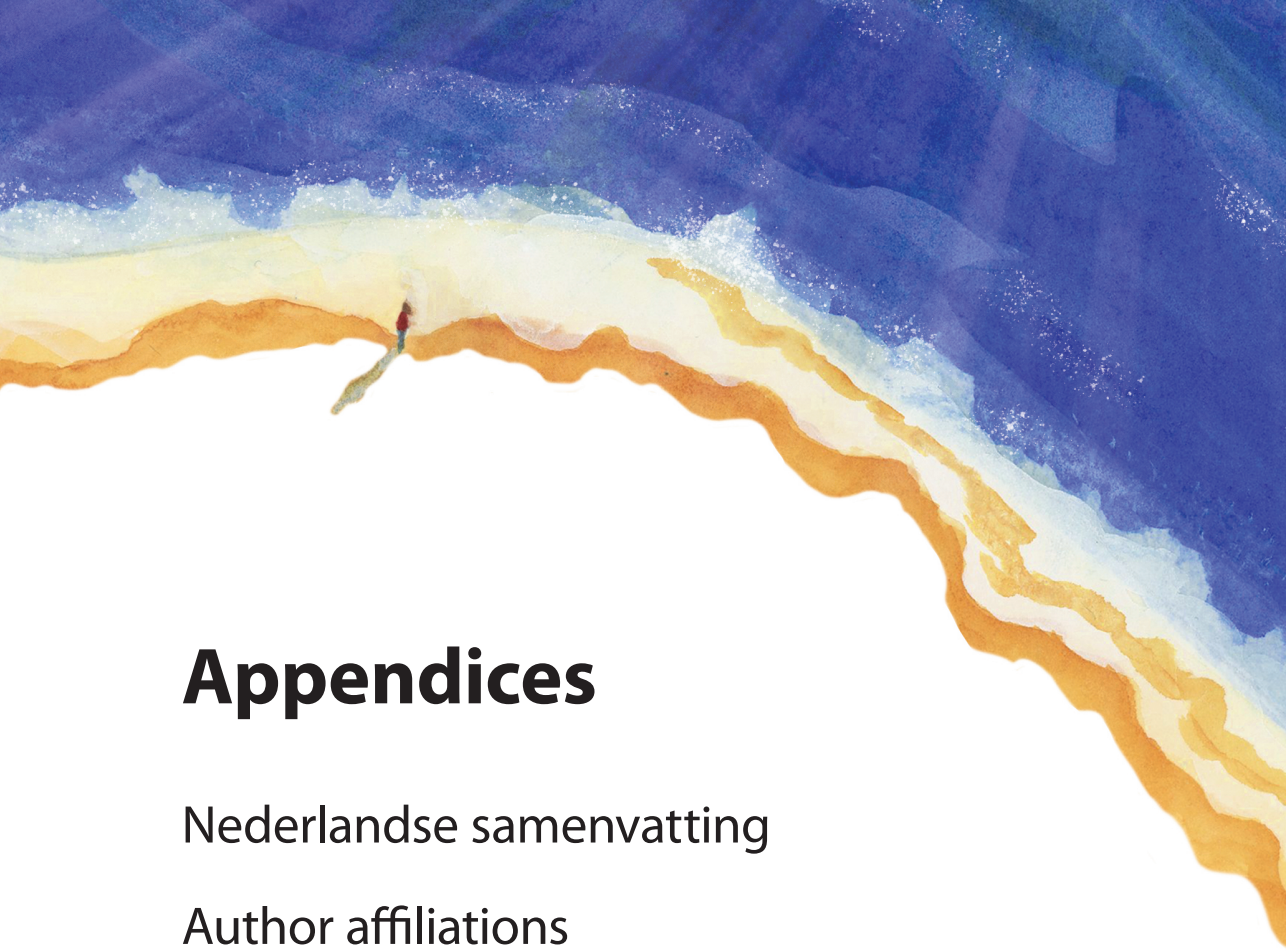

Appendices

Nederlandse samenvatting

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NEDERLANDSE SAMENVATTING

Introductie

Endometriumcarcinoom (baarmoederkanker) is de meest voorkomende gynaecologische kanker in ontwikkelde landen. Door de vergrijzing en de toenemende obesitas onder de bevolking is de incidentie de afgelopen jaren gestegen. In 2017 kregen in Nederland 2025 vrouwen de diagnose endometriumcarcinoom en overleden 493 vrouwen aan deze ziekte. Door het optreden van vroege symptomen zoals postmenopauzaal bloedverlies presenteert de meerderheid van vrouwen zich met een vroeg stadium. Bij ongeveer 30% zijn er intermediaire risicofactoren en slechts 15-20% heeft bij diagnose hoog-risico kenmerken van het endometriumcarcinoom.

De standaard operatie bij vrouwen met endometriumcarcinoom bestaat uit een totale abdominale of laparoscopische hysterectomie met bilaterale salpingo-oophorectomie (TAH/TLH-BSO), en op indicatie wordt een pelviene en/of para-aortale lymfeklierdissectie verricht.

Adjuvante behandeling bij endometriumcarcinoom wordt gegeven om de kans op een recidief te verlagen. De indicatie hiervoor wordt bepaald aan de hand van de risicofactoren van de primaire tumor. Op basis van het stadium, het histologisch type, de tumor graad, diepte van myometrium invasie, leeftijd en lymfangioinvasie (LVSI) worden vrouwen met endometriumcarcinoom onderverdeeld in laag risico, intermediair risico en hoog risico. Stadium I endometriumcarcinoom graad 3 met diepe myometrium invasie en/of met substantiële LVSI wordt als hoog risico beschouwd, evenals stadium II-III endometriumcarcinoom, en non-endometrioïde tumoren zoals sereus en clear cell endometriumcarcinoom.

De PORTEC studies

De Post-Operatieve Radiotherapie bij Endometrium Carcinoom (PORTEC) studies zijn nationale en internationale gerandomiseerde studies voor vrouwen met endometriumcarcinoom. Uit de PORTEC-1 studie is gebleken dat voor stadium I endometriumcarcinoom postoperatieve radiotherapie het risico op een recidief in het bekkengebied significant vermindert, echter zonder verschil in overleving. Sinds de PORTEC-1 studie is de indicatie voor radiotherapie gelimiteerd tot vrouwen met een hoog-intermediair risico, hetgeen tot een reductie in het gebruik van postoperatieve radiotherapie bij vrouwen met endometriumcarcinoom heeft geleid. De tweede PORTEC studie heeft aangetoond dat vaginale brachytherapie (inwendige bestraling) een gelijkwaardig hoge vaginale controle geeft, met minder toxiciteit en een betere kwaliteit van leven vergeleken met uitwendige bestraling van het bekken.

Standaard adjuvante behandeling in Nederland van vrouwen met hoog-risico endometriumcarcinoom bestaat uit uitwendige radiotherapie van het bekkengebied (EBRT). Om

de prognose van deze vrouwen te verbeteren hebben studies adjuvante chemotherapie met EBRT vergeleken. In deze studies werd geen verschil in progressie-vrije of totale overleving gevonden. In retrospectieve series werd een verhoogd risico op bekkenrecidief gevonden na adjuvante behandeling met alleen chemotherapie. Dit was aanleiding voor meerdere groepen om de combinatie van chemotherapie en radiotherapie te onderzoeken. Twee fase III studies hebben vrouwen met hoog-risico endometriumcarcinoom gerandomiseerd tussen EBRT alleen, en EBRT gecombineerd met chemotherapie. Een gecombineerde analyse van deze twee studies liet een significante verbetering in de progressie-vrije overleving en een trend voor een betere totale overleving zien. In deze studies werden verschillende chemotherapie combinaties en verschillende volgorde van chemotherapie en radiotherapie gebruikt. Een fase II pilot studie onder patiënten met hoog-risico endometriumcarcinoom met EBRT met gelijktijdig chemotherapie, gevolgd door adjuvante chemotherapie liet naast veelbelovende resultaten zien dat de gecombineerde behandeling goed verdragen wordt door patiënten. Beide behandelmodaliteiten werden in dit schema dus kort na operatie gestart.
Om de waarde van de combinatie van chemotherapie en radiotherapie bij hoog-risico endometriumcarcinoom te onderzoeken met een eenduidig schema en met goede registratie van toxiciteit en kwaliteit van leven werd de gerandomiseerde, internationale PORTEC-3 studie geïnitieerd. Vrouwen met hoog-risico endometriumcarcinoom werden gerandomiseerd tussen EBRT alleen (RT), of EBRT gecombineerd met 2 gelijktijdige kuren cisplatin, gevolgd door 4 adjuvante kuren carboplatin en paclitaxel (CTRT). In dit proefschrift worden de uitkomsten van de PORTEC-3 studie, alsmede de lange termijn kwaliteit van leven in de PORTEC-2 studie beschreven.

Lange termijn kwaliteit van leven in de PORTEC-2 studie

In de PORTEC-1 studie heeft lange termijn kwaliteit van leven analyse laten zien dat zelfs na 10-15 jaar patiënten die uitwendig bestraald zijn meer frequent darmsymptomen rapporteerden en dat er in de loop van de tijd meer blaasklachten ontstonden vergeleken met patiënten die niet bestraald zijn. Na 5 jaar follow up in de PORTEC-2 studie werd gezien dat patiënten met uitwendige bestraling gemiddeld meer darmklachten hadden dan patiënten die behandeld waren met inwendige bestraling. In hoofdstuk 2 wordt de lange termijn kwaliteit van leven in de PORTEC-2 studie beschreven, 7-10 jaar na deelname in de studie. Deze analyse laat zien dat EBRT een langdurige en klinisch relevante impact heeft. Vrouwen rapporteerden voornamelijk darm-gerelateerde klachten met matig tot ernstige beperking in het dagelijks leven in 10% van de vrouwen. Voornaamste klinisch relevante klachten na behandeling met EBRT waren diarree (8%), gering verlies van ontlasting of strepen in het ondergoed (11%) en verhoogde aandrang (23%). Daarnaast werd op de lange termijn een trend voor meer blaasklachten, zoals fre-

quente aandrang beschreven. Deze symptomen leiden niet tot een significant verschil in algehele gezondheid of totale kwaliteit van leven.

Centrale pathologie revisie

Omdat de indicatie voor adjuvante behandeling voor een groot deel afhangt van de histologische pathologie diagnose is het belangrijk dat dit op eenzelfde, reproduceerbare manier beoordeeld wordt. Eerdere studies hebben laten zien dat voor gynaecologische tumoren vaak sprake is van discordantie tussen twee beoordelingen van een histologisch preparaat. In de PORTEC-1 en PORTEC-2 studie is achteraf revisie van de pathologie preparaten verricht. Na de revisie bleek 23.6% van de patiënten in de PORTEC-1 en 14% van de patiënten in de PORTEC-2 studie achteraf niet aan de inclusiecriteria te voldoen. In de PORTEC-3 studie vormde de beoordeling van de regionale patholoog een eerste indicatie voor geschiktheid voor deze studie, waarna centrale pathologie revisie plaatsvond door een gespecialiseerde gynaecopatholoog. Deze diagnose bepaalde de uiteindelijke geschiktheid en toelating tot de studie. In hoofdstuk 3 worden de resultaten van de vergelijking tussen de lokale en centrale pathologie beoordeling in Nederland en het Verenigd Koninkrijk beschreven. In 43% van de gevallen verschilde de centrale pathologie beoordeling op één of meerdere items ten opzichte van het eerdere verslag. De grootste mate van discrepantie werd gevonden voor histologisch graad en type. Deze discrepanties zorgden er voor dat bij 8% van de revisies de patiënt niet meer in aanmerking kwam voor de PORTEC-3 studie. Het meest frequent was dit door een verschil in het histologisch type, endocervicale stromale betrokkenheid of histologische graad. Door de revisie zijn deze patiënten niet in de studie geïncludeerd, waardoor patienten een potentieel belastende behandeling werd bespaard en de studie populatie uit echte hoog-risico endometriumcarcinoom patiënten bestond.
In de literatuur wordt een betere overeenkomst in pathologische beoordelingen beschreven bij aanvullende immunohistochemische kleuringen, die zeer beperkt werden gebruikt in de PORTEC-3 studie. Tijd en kosten bemoeilijken centrale pathologiebeoordeling, al zal de overgang naar digitale pathologie dit makkelijker maken. Door subspecialisatie in gynaecopathologie, gebruik van immunohistochemische kleuringen en moleculaire analyse zal de discrepantie naar verwachting verder doen afnemen en de risico inschatting verbeteren.

Toxiciteit en kwaliteit van leven in de PORTEC-3 studie

In hoofdstuk 4 worden de kwaliteit van leven en toxiciteit in de PORTEC-3 studie tijdens behandeling en de eerste 2 jaar na randomisatie beschreven. Tijdens de behandeling en de eerste 6 maanden daarna werd bij patiënten die behandeld waren met chemotherapie en radiotherapie significant meer toxiciteit gerapporteerd en werd een verminderde kwaliteit van leven gemeten dan bij patiënten met alleen radiotherapie. Tijdens behan-

deling werd graad ≥3 toxiciteit gerapporteerd door 61% van de patiënten die waren behandeld met CTRT (voornamelijk hematologische toxiciteit) vergeleken met 13% van de patiënten die alleen RT kregen. Zes maanden na randomisatie werd onder de vrouwen die met CTRT behandeld werden een significant slechtere score in het algemeen functioneren en hogere symptoom scores beschreven. Deze scores verbeterden in het eerste jaar: op 12 en 24 maanden na randomisatie was de kwaliteit van leven vergelijkbaar tussen de 2 groepen, alleen het fysiek functioneren was nog iets verminderd in de CTRT groep. Ook qua toxiciteit werd in het eerste jaar na randomisatie duidelijk herstel gezien: na 12 en 24 maanden werd geen significant verschil in graad ≥3 toxiciteit meer gerapporteerd. Het enige symptoom dat significant verschillend bleef op 24 maanden na randomisatie is graad 2 sensorische neuropathie: 10% vs <1% (p<0.0001). Ook een latere, beknopte toxiciteit update (beschreven in Hoofdstuk 6) toont significant meer sensorische neuropathie bij patiënten die met CTRT behandeld zijn, 8% vs 0% (p<0.001) op 60 maanden. Dit werd ook door vrouwen zelf gerapporteerd: 2 jaar na randomisatie gaf 25% van de vrouwen behandeld met CTRT klachten van matig ernstig tot ernstige tintelingen en doof gevoel te hebben, vergeleken met 6% van de vrouwen na alleen RT.

Recidief en overleving in de PORTEC-3 studie

In hoofdstuk 5 worden de primaire uitkomsten totale overleving en recidief vrije overleving beschreven. Omdat de overleving in de PORTEC-3 hoger was dan bij aanvang van de studie werd verwacht en het beoogde aantal events mogelijk pas in of na 2019 gehaald zou worden werd de analyse op basis van follow-up tijd in plaats van het aantal events verricht. Bij een mediane follow-up van 60.2 maanden werd een significant betere 5-jaars recidiefvrije overleving (FFS) gevonden voor vrouwen behandeld met CTRT: 76% na CTRT versus 69% na RT (HR 0.71, p=0.022). Er werd een verschil van 5% in de 5-jaars totale overleving gevonden, dat echter statistisch niet significant was: 82% (CTRT) versus 77% (RT, HR 0.76, p=0.11). Voor de analyse naar de frequentie en type recidieven en de overleving en behandeling na recidief werden de primaire eindpunten met een mediane follow-up van 72 maanden opnieuw geanalyseerd waarbij 75% van de deelnemende vrouwen 5 jaar follow up heeft bereikt. Deze analyse is beschreven in hoofdstuk 6. Deze geüpdate (post-hoc) analyse laat een statistisch significante verbetering van zowel de overleving als de recidief vrije overleving zien met de combinatie van chemotherapie en radiotherapie vergeleken met radiotherapie alleen: 5% verbetering in totale overleving (HR 0.70, p=0.034) en 7% in recidief vrije overleving (HR 0.70, p=0.016). Bij de meeste vrouwen was in de PORTEC-3 studie het eerste recidief een metastase op afstand; een geïsoleerd recidief in de vagina of bekken was zeldzaam. De lokale controle was in beide armen hoog, wat verklaard kan worden door het geven van EBRT in beide behandelarmen. Vrouwen in de radiotherapie arm van de studie werden voor hun eerste

recidief vaker met chemotherapie behandeld. De overleving na een recidief was 1.4 jaar en was niet significant verschillend tussen de beide armen.

Omdat hoog-risico endometriumcarcinoom een heterogene groep patiënten omvat, van zowel vroeg stadium endometrioïd endometriumcarcinoom met ongunstige prognostische kenmerken, hogere stadia, als non-endometrioïde tumoren zoals sereus en clear cell carcinoom, worden in hoofdstuk 6 subgroep analyses naar stadium en histologisch type beschreven.
Vrouwen met stadium III endometriumcarcinoom hadden een significant hoger risico op recidief of overlijden vergeleken met vrouwen met stadium I-II ziekte, ongeacht behandeling. Voor vrouwen met stadium I-II ziekte bleek de winst van toevoeging van chemotherapie beperkt: 2% absolute winst in totale overleving en 4% absolute winst in recidief-vrije overleving. Voor vrouwen met stadium III endometriumcarcinoom werd echter een verbetering in totale en recidief-vrije overleving gevonden van respectievelijk 10% en 12.5% absoluut verschil in het voordeel van de combinatie van radiotherapie en chemotherapie.
Uitgesplitst naar histologisch type, hebben vrouwen met sereus type endometriumcarcinoom de slechtste prognose vergeleken met vrouwen met andere histologische typen. Deze patiënten bleken een groot voordeel van de toevoeging van chemotherapie aan radiotherapie te hebben met 19% absoluut voordeel in totale overleving (71.4% vs 52.8%) en 12% in recidief-vrije overleving (59.7% vs 47.9%).

Discussie

In Hoofdstuk 7 worden de belangrijkste bevindingen in het perspectief van de bestaande literatuur geplaatst en worden de belangrijke vraagstukken en toekomstperspectief besproken. Twee Amerikaanse studies van de Gynecologic Oncology Group (GOG) die gelijktijdig met de PORTEC-3 patiënten hebben geïncludeerd zijn de GOG-249 en 258. In de GOG-249 zijn vrouwen met stadium I-II endometriumcarcinoom met hoog(-intermediair) risico gerandomiseerd tussen EBRT alleen versus vaginale brachytherapie (VBT) gevolgd door 3 kuren carboplatin en paclitaxel. De combinatie van VBT en chemotherapie gaf geen verbetering van progressie-vrije overleving, noch van de totale overleving, terwijl significant meer lymfklier recidieven in het bekken en/of para-aortaal werden gezien. Voor deze groep patiënten met stadium I-II endometriumcarcinoom lijkt op basis van de PORTEC-3 en GOG-249 studies de winst van toevoeging van chemotherapie te beperkt te zijn om de toename in bijwerkingen en de verminderde kwaliteit van leven te rechtvaardigen. Derhalve blijft het advies voor deze groep van patiënten postoperatieve uitwendige bestraling van het bekkengebied.
In de GOG-258 studie werden vrouwen met stadium III-IV endometriumcarcinoom gerandomiseerd tussen dezelfde combinatie van EBRT en chemotherapie als in de

PORTEC-3 studie, versus alleen chemotherapie (6 kuren carboplatin en paclitaxel). Er werd geen verschil gevonden in recidief-vrije overleving, noch in totale overleving. Er werden ook in deze studie significant meer lymfekliermetastasen in het bekken en/of para-aortaal en vaginale recidieven gezien in de groep die alleen chemotherapie kreeg. Gebaseerd op de GOG-258 en PORTEC-3 studie lijkt de combinatie van chemotherapie en radiotherapie voor patiënten met stadium III endometriumcarcinoom te zorgen voor een optimale recidief-vrije overleving met een goede locoregionale controle.

Toekomstperspectieven

Belangrijk voor de toekomstige behandeling zijn een betere selectie en het individualiseren van adjuvante behandeling. Gezien de heterogeniteit van het hoog-risico endometriumcarcinoom is het waarschijnlijk dat het voordeel van chemotherapie meer uitgesproken zal zijn bij specifieke patiëntengroepen. In 2013 publiceerde 'The Cancer Genome Atlas' groep (TCGA) een nieuwe indeling van endometriumcarcinoom op basis van moleculair-genetische kenmerken en de belangrijkste 'driver' mutatie: (1) de groep met polymerase-epsilon (POLE) mutatie, (2) de groep met mismatch repair deficiëntie (MRD), (3) de groep met TP53 mutatie, en (4) een 'copy number low' groep zonder specifieke moleculaire kenmerken (NSMP). Deze vier groepen hebben een sterke prognostisch voorspellende waarde en kunnen in combinatie met andere risicofactoren als L1-CAM overexpressie, substantiële LVSI en CTNNB1-mutatie de kans op recidief beter voorspellen. Dit geïntegreerde moleculaire profiel wordt momenteel prospectief getest in de gerandomiseerde PORTEC-4a studie. In deze studie worden patiënten met hoog-intermediair risico stadium I-II endometriumcarcinoom gerandomiseerd (1:2) tussen standaard vaginale brachytherapie (VBT) en adjuvante behandeling gebaseerd op een moleculair geïntegreerd risicoprofiel.

Ook bij het hoog-risico endometriumcarcinoom is uit een pilot studie gebleken dat de TCGA moleculaire subgroepen een sterk onderscheid maken tussen patiënten met een (zeer) gunstige prognose (POLE-mutant), intermediaire prognose (MRD), wat minder gunstige prognose (NSMP), en degenen met een ongunstige prognose (P53-mutant). In de PORTEC-3 studie is van bijna 65% van de internationale patiënten FFPE weefselmateriaal verzameld in een gemeenschappelijke biobank, waarop de komende jaren translationeel onderzoek zal worden verricht binnen het TransPORTEC consortium. Uitgebreide moleculaire analyse van dit groot, prospectief gerandomiseerd cohort hoog-risico endometriumcarcinoom patiënten met complete follow-up zal veel informatie geven over de prognostische waarde van de moleculaire subgroepen, waarbij ook het effect van adjuvante chemotherapie op de specifieke groepen zal worden bekeken. Daarnaast zal er gezocht worden naar moleculaire veranderingen of andere kenmerken zoals DNA repair afwijkingen en genoom instabiliteit die voor gerichte (targeted) therapie gebruikt kunnen worden.

De afgelopen jaren is de techniek van bestraling sterk verbeterd waarbij de dosis aan de omliggende organen steeds meer beperkt kan worden. Dit is belangrijk om de bijwerkingen tijdens de bestraling maar ook op de lange termijn zoveel mogelijk te beperken. Met de ontwikkelingen in de beeldgestuurde radiotherapie en onderzoek naar protonentherapie voor gynaecologische tumoren zal in de nabije toekomst een verdere verbetering van de bestraling-gerelateerde bijwerkingen te verwachten zijn. Samen met een betere risicostratificatie kan dit er toe leiden dat minder patiënten worden blootgesteld aan onnodige bijwerkingen van de behandeling.

Deze factoren zijn belangrijk omdat endometriumcarcinoom een ziekte is die voornamelijk oudere vrouwen betreft en deze patiënten frequent comorbiditeiten hebben zoals obesitas, hypertensie en andere cardiovasculaire aandoeningen. Met iedere patiënt moet daarom de afweging worden gemaakt tussen de winst in progressie-vrije en totale overleving aan de ene kant, en de toename in bijwerkingen, verminderde kwaliteit van leven en (veel) langere behandelduur aan de andere kant. Translationeel onderzoek zal in de nabije toekomst meer informatie geven over de moleculaire kenmerken van hoog-risico endometriumcarcinoom en de respons op chemotherapie, en dit zal artsen en patiënten verder helpen in de besluitvorming. Door de integratie van moleculaire kenmerken in het risicoprofiel kan de risico-inschatting verbeterd worden en zal de adjuvante behandeling verder geïndividualiseerd worden.

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LIST OF PUBLICATIONS AND CONFERENCE PRESENTATIONS

Publications

de Boer, S.M., M.E. Powell, L. Mileshkin, D. Katsaros, P. Bessette, C. Haie-Meder, P.B. Ottevanger, J.A. Ledermann, P. Khaw, R. D'Amico, A. Fyles, M.H. Baron, I.M. Jurgenliemk-Schulz, H.C. Kitchener, H.W. Nijman, G. Wilson, S. Brooks, S. Gribaudo, D. Provencher, C. Hanzen, R.F. Kruitwagen, V. Smit, N. Singh, V. Do, A. Lissoni, R.A. Nout, A. Feeney, K.W. Verhoeven-Adema, H. Putter, C.L. Creutzberg; Patterns of recurrence and updated survival outcomes in the randomised PORTEC-3 trial of adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer; Lancet Oncol. Epub 22 July 2019

de Boer, S.M., R.A. Nout, C.L. Creutzberg; Adjuvante behandeling van hoog-risico endometriumcarcinoom: update van recente gerandomiseerde trials; NTVO. Accepted.

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de Graaf, F.R., J.E. van Velzen, **S.M. de Boer**, J.M. van Werkhoven, L.J. Kroft, A. de Roos, A. Sieders, G.J. de Grooth, J.W. Jukem.a, J.D. Schuijf, J.J. Bax, M.J. Schalij, E.E van der Wall; Non-invasive computed tomography coronary angiography as a gatekeeper for invasive coronary angiography Int J Cardiovasc Imaging. 2012 May 11

van Werkhoven J.M.* MSc, **S.M. de Boer***, J.D. Schuijf, F. Cademartiri, E. Maffei, J.W. Jukema, M.J. Boogers, L.J. Kroft, A. de Roos, J.J. Bax; Impact of Clinical Presentation and Pre-Test Likelihood on the Relation between Calcium Score and Computed Tomography Coronary Angiography; Am J Cardiol. 2010 Dec 15;106(12):1675-9. Epub 2010 Nov 4)
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Conference presentations

American Society for Radiation Oncology (ASTRO) annual meeting 2019 (oral presentation)
de Boer, S.M., M.E. Powell, L. Mileshkin, D. Katsaros, P. Bessette, C. Haie-Meder, P.B. Ottevanger, J.A. Ledermann, P. Khaw, A. Colombo, A. Fyles, M-H. Baron, I.M. Jürgenliemk-Schulz, H.C. Kitchener, H.W. Nijman, R.F. Kruitwagen, V.T. Smit, R.A. Nout, H. Putter, C.L.

Creutzberg; Patterns of recurrence and survival in the randomized PORTEC-3 trial of chemoradiotherapy for high-risk endometrial cancer.

Gynaecology congress of the Dutch Society of Obstetrics and Gynaecology (NVOG) 2019 (oral presentation)
de Boer, S.M., M.E. Powell, L. Mileshkin, D. Katsaros, P. Bessette, C. Haie-Meder, P.B. Ottevanger, J.A. Ledermann, P. Khaw, A. Colombo, A. Fyles, M-H. Baron, I.M. Jürgenliemk-Schulz, H.C. Kitchener, H.W. Nijman, R.F. Kruitwagen, V.T. Smit, R.A. Nout, H. Putter, C.L. Creutzberg; Update of survival outcomes in the PORTEC-3 trial

European Society Radiation Oncology (ESTRO) annual meeting 2018 (oral presentation)
de Boer, S.M., M.E. Powell, L. Mileshkin, D. Katsaros, P. Bessette, C. Haie-Meder, P.B. Ottevanger, J.A. Ledermann, P. Khaw, A. Colombo, A. Fyles, M.H. Baron, I.M. Jürgenliemk-Schulz, H.C. Kitchener, H.W. Nijman, G. Wilson, I. Kolodziej, S. Carinelli, L.C.H.W. Lutgens, V.T.H.B.M. Smit, N. Singh, R.A. Nout, K.W. Verhoeven-Adema, H. Putter, C.L. Creutzberg; OC-0323: Patterns of recurrence in the randomised PORTEC-3 trial of chemoradiotherapy for endometrial cancer.

European Congress of Pathology (ECP) annual meeting 2017 (oral presentation)
de Boer, S.M., B.G. Wortman, T. Bosse, M.E. Powell, N. Singh, H. Hollema, G. Wilson, M.N. Chowdhury, L. Mileshkin, J. Pyman, D. Katsaros, S. Carinelli, A. Fyles, C.M. McLachlin, C. Haie-Meder, P. Duvillard, R.A. Nout, K.W. Verhoeven-Adema, H. Putter, C.L. Creutzberg, V. Smit; Upfront pathology review in the randomised PORTEC-3 trial for high risk endometrial cancer.

Scientific meeting of the Dutch Society for Radiotherapy and Oncology (NVRO) 2017 (oral presentation)
de Boer, S.M., B.G. Wortman, T. Bosse, M.E. Powell, N. Singh, H. Hollema, G. Wilson, M.N. Chowdhury, L. Mileshkin, J. Pyman, D. Katsaros, S. Carinelli, A. Fyles, C.M. McLachlin, C. Haie-Meder, P. Duvillard, R.A. Nout, K.W. Verhoeven-Adema, H. Putter, C.L. Creutzberg, V. Smit; The value of upfront pathology review in the PORTEC-3 trial.

American Society of Clinical Oncology (ASCO) annual meeting 2017 (oral presentation)
de Boer, S.M., M.E. Powell, L.R. Mileshkin, D. Katsaros, P. Bessette, C. Haie-Meder, P.B. Ottevanger, J.A. Ledermann, P. Khaw, A. Colombo, A.W. Fyles, M-H. Baron, H.C. Kitchener, H.W. Nijman, R.F.P.M. Kruitwagen, I.M. Jurgenliemk-Schulz, R.A. Nout, V.T.H.B.M. Smit, H. Putter, C.L. Creutzberg; Final results of the international randomized PORTEC-3 trial of adjuvant chemotherapy and radiation therapy (RT) versus RT alone for women with high-risk endometrial cancer.

International Gynecologic Cancer Society (IGCS) biannual meeting 2016 (poster)
de Boer, S.M., B.G. Wortman, T. Bosse, M.E. Powell, N. Singh, H. Hollema, G. Wilson, M.N. Chowdhury, L. Mileshkin, J. Pyman, D. Katsaros, S. Carinelli, A. Fyles, C.M. McLachlin, C. Haie-Meder, P. Duvillard, R.A. Nout, K.W. Verhoeven-Adema, H. Putter, C.L. Creutzberg, V. Smit; Clinical consequences of upfront pathology review in the randomised PORTEC-3 trial for high risk endometrial cancer.

Dutch Gynaecology Oncology Group symposium 2016 (oral presentation)
de Boer, S.M., M.E. Powell, L. Mileshkin, D. Katsaros, P. Bessette, C. Haie-Meder, R.A. Nout, H.C. Kitchener, P.B. Ottevanger, P. Khaw, A. Colombo, A. Fyles, M-H. Baron, H.W. Nijman, R. Kruitwagen , J.A. Ledermann , K.W. Verhoeven-Adema, V.T. Smit, H. Putter, C.L. Creutzberg; Toxicity and quality of life after adjuvant chemotherapy and radiation therapy (RT) versus RT alone for women with high-risk endometrial cancer: first results of the randomised PORTEC-3 trial.

Scientific meeting of the Dutch Society for Radiotherapy and Oncology (NVRO) 2015 (oral presentation)
de Boer, S.M., M.E. Powell, L. Mileshkin, D. Katsaros, P. Bessette, C. Haie-Meder, R.A. Nout, H.C. Kitchener, P.B. Ottevanger, P. Khaw, A. Colombo, A. Fyles, M-H. Baron, H.W. Nijman, R. Kruitwagen , J.A. Ledermann , K.W. Verhoeven-Adema, V.T. Smit, H. Putter, C.L. Creutzberg; Toxicity and quality of life after adjuvant chemotherapy and radiation therapy (RT) versus RT alone for women with high-risk endometrial cancer: first results of the randomised PORTEC-3 trial.

European Society Gynaecologic Oncology (ESGO) biannual meeting 2015 (poster)
de Boer, S.M., M.E. Powell, L. Mileshkin, D. Katsaros, P. Bessette, C. Haie-Meder, R.A. Nout, H.C. Kitchener, P.B. Ottevanger, P. Khaw, A. Colombo, A. Fyles, M-H. Baron, H.W. Nijman, R. Kruitwagen , J.A. Ledermann , K.W. Verhoeven-Adema, V.T. Smit, H. Putter, C.L. Creutzberg; Relation between patient and physician reported toxicity in the randomised PORTEC-3 trial of radiation therapy (RT) with or without chemotherapy for endometrial cancer.

European Society Radiation Oncology (ESTRO) annual meeting (poster presentation)
de Boer, S.M., R.A. Nout, H. Putter, I.M. Jürgenliemk-Schulz, J.J. Jobsen, L.C.H.W. Lutgens, E.M. Van der Steen-Banasik, J.W.M. Mens, A. Slot, M.C. Stenfert Kroese, H.W. Nijman, C.L. Creutzberg; Long-term bowel and bladder symptoms after pelvic radiotherapy or vaginal brachytherapy in the PORTEC-2 trial.

CURRICULUM VITAE

Stephanie de Boer werd op 28 november 1986 geboren in Naarden. In 2005 behaalde zij haar Gymnasium diploma aan het Willem de Zwijgercollege te Bussum, waarna zij startte met de studie geneeskunde aan de Universiteit Leiden. Tijdens haar studie heeft zij een klinische stage (interne geneeskunde) gevolgd in het Dr. Moewardi Hospital in Surakarta, Indonesie, en heeft zij haar laatste keuzecoschap tropengeneeskunde in het St Joseph Hospital, Kagondo, Tanzania, afgerond. In 2009 heeft zij wetenschappelijke stage gedaan op de afdeling Cardiologie in het Leids Universitair Medisch Centrum. Na het behalen van haar artsexamen in 2012 (cum laude) heeft ze een jaar in het Bronovo ziekenhuis te Den Haag gewerkt als arts-assistent (ANIOS) op de afdeling interne geneeskunde.

In oktober 2013 is zij gestart met de opleiding tot Radiotherapeut-Oncoloog in het Leids Universitair Medisch Centrum (opleiders: prof. dr. C.A.M. Marijnen en prof dr. C.L. Creutzberg), en gedurende 14 maanden in het Haaglanden Medisch Centrum (opleiders: dr. R. Wiggenraad en dr. A.Y. Verbeek-de Kanter). Tijdens haar opleiding startte zij in 2014 met onderzoek naar de lange termijn kwaliteit van leven in de PORTEC-2 studie en naar de uitkomsten van de PORTEC-3 studie onder begeleiding van prof. dr. C.L. Creutzberg en dr. R.A. Nout. In 2016 heeft zij in het Verenigd Koninkrijk (Barts and the London NHS Trust, London en Manchester Royal Infirmary Hospital, Manchester, begeleider dr. N. Singh) onderzoek gedaan naar de centrale pathologie revisie in de PORTEC-3 studie, waarvoor zij een reisbeurs van het Leids Universiteits Fonds ontving. In het kader van de studies in dit proefschrift bezocht ze diverse congressen in het binnen- en buitenland waar ze meerdere presentaties gaf.

Stephanie zal op 31 december 2019 haar opleiding afronden en zij zal per 1 januari 2020 starten als Radiotherapeut-Oncoloog in het Leids Universitair Medisch Centrum. Dit zal zij blijven combineren met onderzoek binnen de gynaecologiegroep, het PORTEC- en het TransPORTEC consortium.

Stephanie is getrouwd met Jesse Bank en samen hebben zij een dochter, Mila.

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