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Radiotherapy for endometrial cancer: improved patient selection, techniques and outcomes

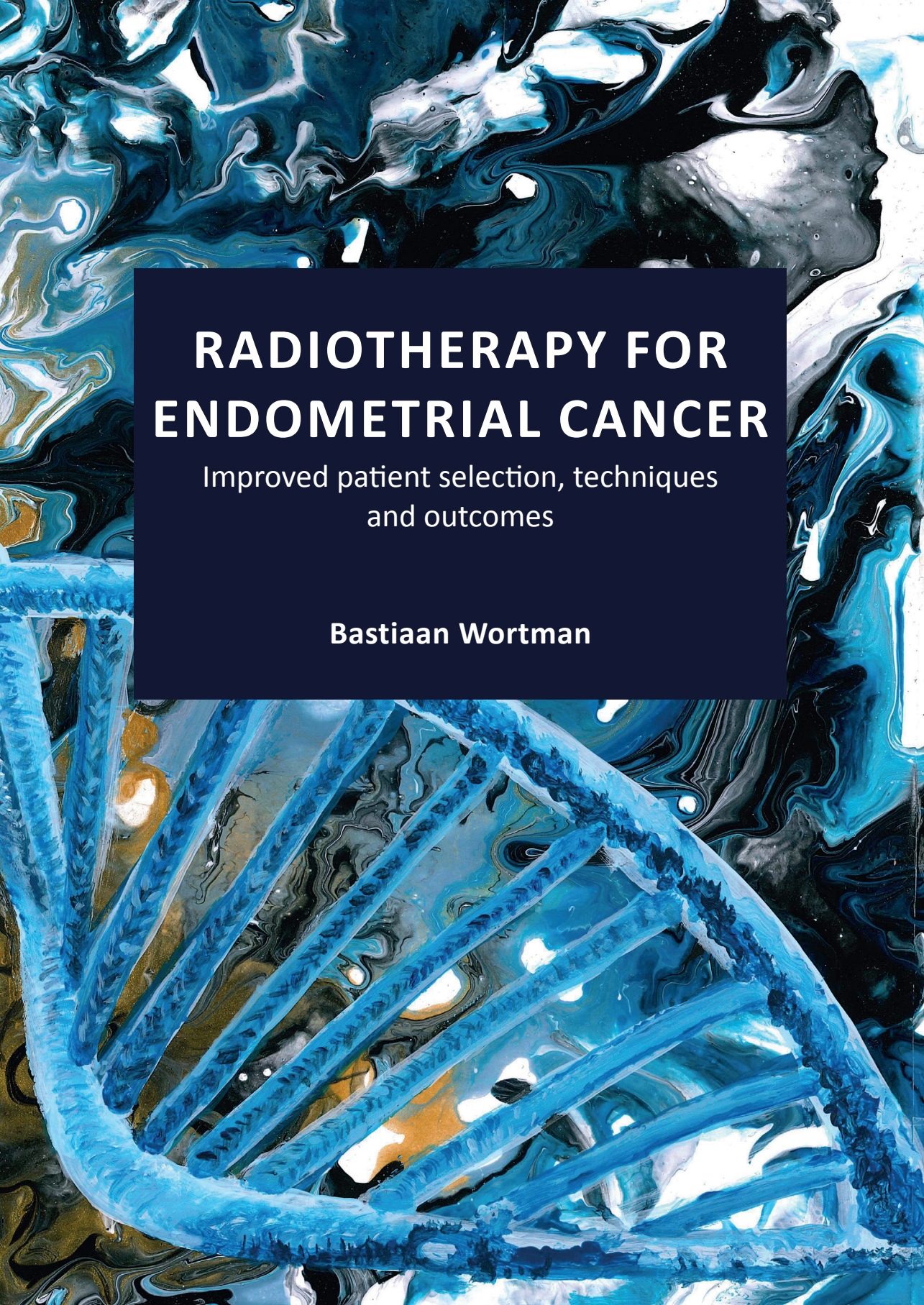
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RADIOTHERAPY FOR ENDOMETRIAL CANCER

Improved patient selection, techniques and outcomes

Bastiaan Wortman

Radiotherapy for endometrial cancer:

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Radiotherapy for endometrial cancer

Improved patient selection, techniques and outcomes

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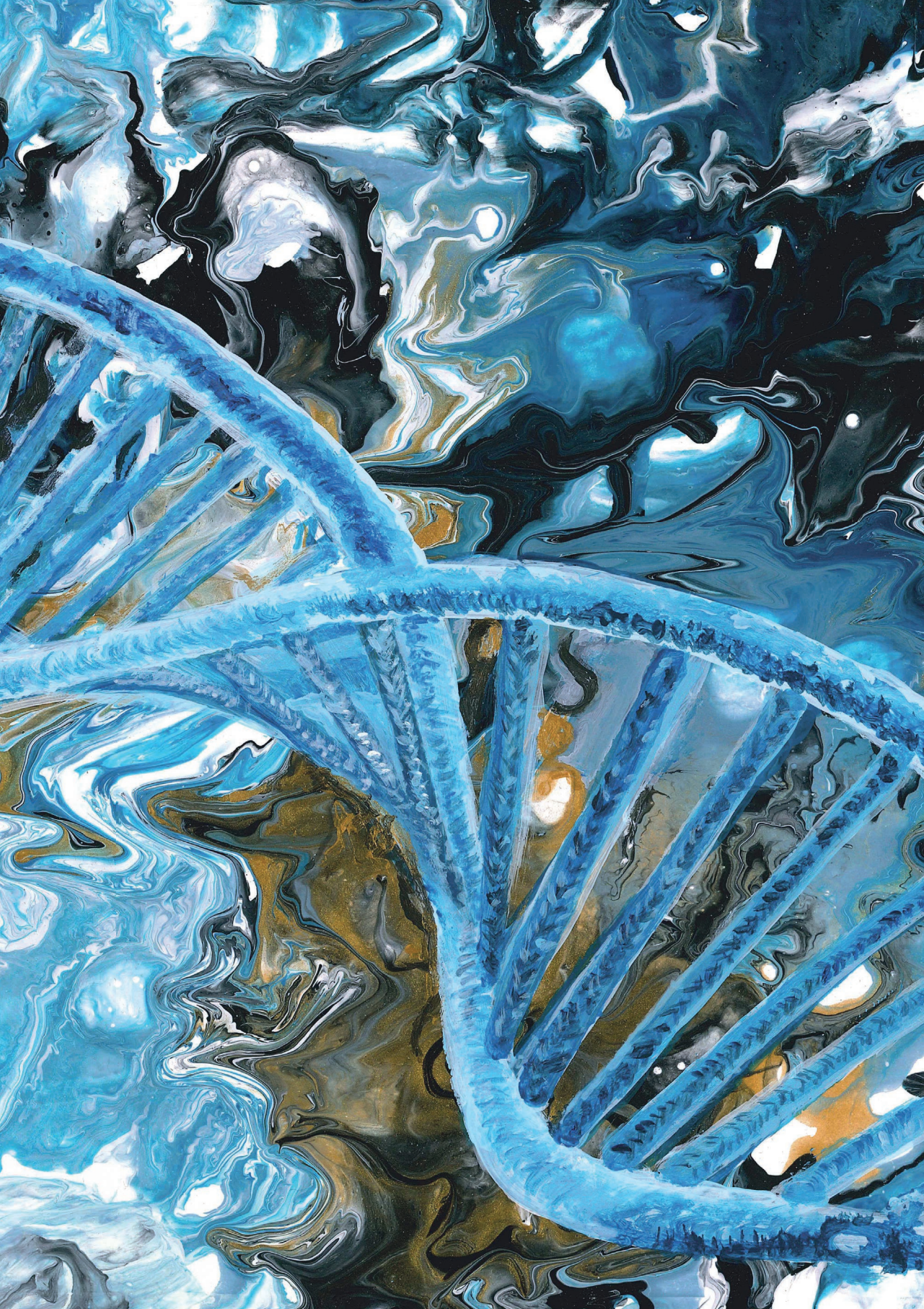
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1

CHAPTER 1

GENERAL INTRODUCTION AND THESIS OUTLINE

Adapted from:
B.G. Wortman, R.A. Nout, T. Bosse and C.L. Creutzberg
Selecting adjuvant treatment for endometrial carcinoma using molecular risk factors

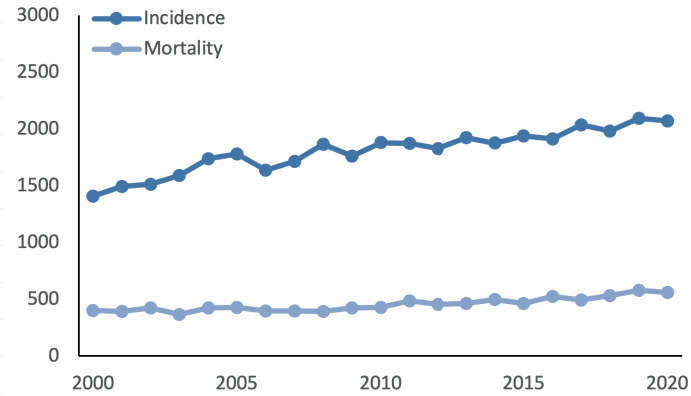
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1. INTRODUCTION

1.1 Epidemiology

Endometrial cancer is the most common gynaecological cancer in developed countries, with the highest incidence in postmenopausal women between 65 and 85 years of age. The incidence is rising due to increased prevalence of diabetes and obesity, and ageing of the population.[1, 2] In The Netherlands in 2020, the estimated number of new endometrial cancer cases was 2069 with 559 cancer-related deaths (*Figure 1*).[3] Most women with endometrial cancer are diagnosed at early stage of disease, due to early symptoms such as vaginal bleeding. This generally results in a favourable prognosis and a relatively low number of cancer-related deaths.[4]

Figure 1. Incidence and mortality of endometrial cancer in the Netherlands.[3]



1.2 Histology and risk factors

Endometrial cancer is diagnosed by physical and pelvic examination, including transvaginal ultrasound, and pathology assessment of a biopsy, curettage or hysterectomy. The most common histological type is endometrioid adenocarcinoma, accounting for approximately 70-80% of endometrial cancers. Non-endometrioid cancers mainly comprise serous and clear cell cancers, accounting for approximately 5-10% and 1-5% of endometrial cancers, respectively, and the other aggressive subtypes are undifferentiated endometrial cancer and uterine carcinosarcomas. Well-established clinicopathological risk factors, used in the current treatment guidelines, are age, histological type, tumour grade, International Federation of Gynaecology and Obstetrics (FIGO)-stage (*Table 1*), depth of myometrial invasion and presence and extent of lymph-vascular space invasion (LVSI).[5, 6] Endometrioid endometrial cancer is usually graded using the FIGO grading system: low grade (grade 1), intermediate grade (grade 2) or high grade (grade 3) based on the

proportion of solid growth and nuclear atypia, while non-endometrioid endometrial cancers are high grade by definition. More recently, a binary grading system has been suggested, separating low-grade (FIGO grade 1 and 2) and high-grade (FIGO grade 3) endometrial cancer which seems more in line with their outcome.[7, 8]

1.3 Pathology

To determine the pathological risk factors of endometrial cancer, multiple features of pathology assessment are needed, and reproducibility is essential to ensure completeness and accuracy of the diagnosis. However, the female reproductive tract has been described as one of the organ systems with the highest inter-observer variation between pathologists.[9] Previous studies reported that a limited proportion of the reviewed pathology specimen resulted in major discrepancies, ranging from 8% to 12%.[10] Pathology review within the PORTEC-1 and 2 trials has shown that 24% and 14% of included patients were, in retrospect, not eligible for the trial.[11-13] Most frequent discrepancies were observed in histological grade, suggesting that a two-tiered grading system (low- versus high grade) could be beneficial.[14] In another inter-observer pathology study on high-grade endometrial cancer, histological subtyping was also a common discrepancy.[15] Pathology review in daily clinical practice could result in a reduction of over- and undertreatment. In the PORTEC-3 trial, upfront pathology review was performed to verify whether patients were truly eligible and would not receive unnecessary toxic treatment. Challenges of standard pathology review are that it can be time-consuming, costly, and comes with logistical difficulties.

Table 1. FIGO 2009 staging of endometrial cancer.[5]

Stage	Description
I	Tumour confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
II	Tumour invades cervical stroma, but does not extend beyond the uterus
III	Local and/or regional spread of the tumour
IIIA	Invasion of the serosa of the corpus uteri 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 lymph nodes with/without positive pelvic lymph nodes
IV	Tumour invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

1.4 Treatment

Standard treatment for women with endometrial cancer is surgery, consisting of laparoscopic or abdominal hysterectomy and bilateral salpingo-oophorectomy, with or without lymph node evaluation. With lymphadenectomy the nodal status can be assessed, and FIGO stage can be assigned adequately. However, routinely performed lymphadenectomy in early stage endometrial cancer remains controversial, as two large randomised trials have shown no improvement in overall survival or disease free survival in early stage endometrial cancer, while there is an increased risk of treatment related morbidity, mostly lymphoedema.[16-18] More recently sentinel node biopsy has emerged as a reliable method for lymph node evaluation, which has been investigated in several studies and has shown to have high sensitivity with lower risk of toxicity.[19-22]

1.5 Adjuvant Treatment

The current guidelines for adjuvant treatment of endometrial cancer are based on the clinicopathologic factors age, FIGO stage, histologic type and grade, myometrial invasion and the presence of LVSI. Based on the clinicopathological risk factors, four risk groups (low, intermediate, high-intermediate and high risk) have been defined, with each risk group having a different prognosis (*Table 2*).[6]

Table 2. Risk groups in endometrial cancer according to PORTEC and the ESMO-ESGO-ESTRO guideline.

Risk Group	PORTEC (2002-2013)[11]	ESMO-ESGO-ESTRO guideline 2021[64]
Low	FIGO stage IA EEC: grade 1-2	FIGO stage IA EEC: grade 1-2, LVSI neg.
Intermediate	FIGO stage IB EEC: grade 1-2, age <60	FIGO stage IB EEC: grade 1-2, LVSI neg.
		FIGO stage IA EEC: grade 3, LVSI neg.
		FIGO stage IA NEEC: no myometrial invasion
High-intermediate	FIGO stage IA EEC: grade 3, age ≥60	FIGO stage IA/B EEC: grade 1-3, LVSI pos.
	FIGO stage IB EEC: grade 1-2, age ≥60	FIGO stage IB EEC: grade 3, LVSI neg.
		FIGO stage II EEC
High	FIGO stage IB EEC: grade 3	FIGO stage III-IVA EEC without residual disease
	FIGO stage II-III EEC	FIGO stage I-IVA NEEC: without residual disease
	FIGO stage I-III NEEC	

EEC endometrioid endometrial cancer; LVSI lymph-vascular space invasion (neg.: negative, pos.: substantial LVSI); NEEC non-endometrioid endometrial cancer (serous or clear cell carcinoma)

Low risk

Previous studies have shown that women with low-risk endometrial cancer have a very low risk of locoregional or distant recurrences. Even without adjuvant radiotherapy, a 5-year disease-free survival of 95% has been reported.[13, 23-25] For this risk group, no adjuvant treatment is recommended.

Intermediate and high-intermediate risk

In the PORTEC-1 and GOG-99 trials women with intermediate risk endometrial cancer were randomised to pelvic external beam radiotherapy (EBRT) versus no adjuvant treatment. Results showed that EBRT significantly reduced locoregional recurrences, without a survival benefit.[13, 24, 26] In the observation group, 75% of the locoregional recurrences were located at the vaginal vault, and with salvage radiotherapy with vaginal brachytherapy survival rates of up to 65% at 5 years could still be reached.[13, 24, 27] These trials led to a reduction of the indication for adjuvant treatment, limiting this to women with high-intermediate risk factors (*Table 2*). As most locoregional recurrences were located at the vaginal vault and there was no survival benefit after pelvic EBRT, vaginal brachytherapy was investigated for women with high-intermediate risk endometrial cancer in the PORTEC-2 trial. Results showed that both vaginal brachytherapy and EBRT were equally effective and had a vaginal control rate of 98% at 5 years without differences in overall and disease-free survival. Women who received vaginal brachytherapy however, had less toxicity and improved quality of life.[28-30] Based on these findings, adjuvant vaginal brachytherapy became the standard adjuvant treatment for women with high-intermediate risk endometrial cancer. However, for women at lower risk of recurrence (age below 60) no adjuvant treatment can also be considered as effective salvage treatment is available.

In the recent years, more knowledge has been gained on risk factors for disease recurrence in endometrial cancer, such as LVSI. In a study of the combined data of the PORTEC-1 and 2 trials, LVSI scored as substantial in a three-tiered scoring system (no, focal or substantial LVSI) showed to be the strongest independent prognostic factor for pelvic and distant metastasis and overall survival.[31, 32] A Swedish nationwide study reported similar findings, even for women that were adequately staged and node negative, the presence of substantial ('obvious') LVSI was associated with decreased overall survival.[33] To lower the risk of distant metastasis, the addition of 3 cycles of chemotherapy to vaginal brachytherapy was investigated and compared to EBRT in the GOG-249 trial. Results showed that there were no significant differences in recurrence-free and overall survival. However, more pelvic and para-aortal nodal recurrences were observed in the arm with vaginal brachytherapy and chemotherapy, even though these women were surgically staged and node negative. In the combined PORTEC-1 and 2 analysis the risk of pelvic metastases was also reduced by pelvic EBRT as compared to vaginal brachytherapy. This could imply that pelvic EBRT should be considered for women with risk factors such as substantial LVSI.[31-33]

High risk

Women with high-risk endometrial cancer are at higher risk of pelvic and distant metastases and endometrial cancer related death.[34-36] In the current treatment guidelines these women receive

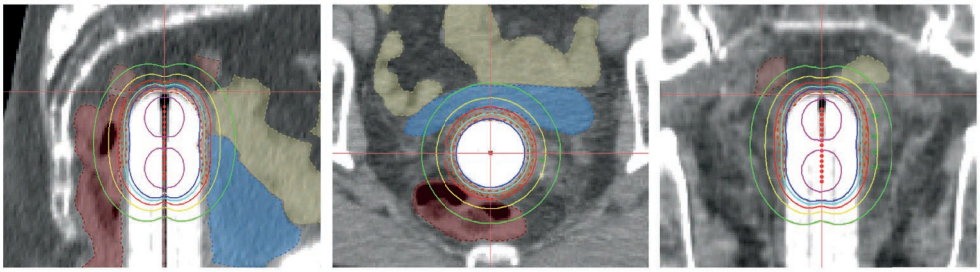
pelvic external beam radiotherapy with or without adjuvant chemotherapy. The role of adjuvant chemotherapy, in combination with EBRT, has been the subject of several randomised trials. The PORTEC-3 trial investigated radiotherapy alone versus radiotherapy combined with chemotherapy (two cycles of cisplatin during radiotherapy followed by four cycles of carboplatin-paclitaxel) for women with high-risk endometrial cancer. Results showed improved recurrence-free and overall survival after combined radiotherapy and chemotherapy compared to radiotherapy alone, at the cost of increased toxicity. Radiotherapy combined with chemotherapy was mainly recommended for stage III disease and serous type cancers.[37-40] Chemotherapy alone could be considered, based on the findings of the GOG-258 trial that investigated radiotherapy combined with chemotherapy versus chemotherapy (six cycles of carboplatin-paclitaxel) alone for women with stage III-IV endometrial cancer. Results showed similar relapse-free survival rates, but increased rates of pelvic and peri-aortic relapses with chemotherapy alone.[41]

1.6 Radiotherapy techniques

Vaginal brachytherapy

Vaginal brachytherapy is a highly effective adjuvant radiotherapy treatment for women with intermediate to high-intermediate risk endometrial cancer, with 5-year vaginal control rates of over 95%.[12, 42-44] Radiation dose is generally administered with high-dose rate (HDR) in three to four fractions of 6 to 7 Gray (Gy), usually by a single channel vaginal cylinder, starting within 6 (-8) weeks from surgery. For specific indications, multichannel cylinders are available with enable MRI-based optimization of the dose distribution and/or local boosts. Brachytherapy planning is based on delineation of the target volume and organs-at-risk on CT or MR-images with the cylinder in situ during at least one fraction to provide data on dose distribution to the clinical target volume and organs-at-risk (*Figure 2*). These data are used to avoid added toxicity to the bladder, rectum and small bowel, even though toxicity of vaginal brachytherapy is mild. Within the PORTEC-2 trial, patients who received vaginal brachytherapy had significantly lower rates of grade 1-2 gastro-intestinal toxicity during treatment compared to those receiving EBRT (12.0% versus 53.8%, $p<0.05$). At 1 and 2 years still significant differences were observed (9.3% and 8.0% versus 22.2% and 17.4%, $p <0.05$). Analysis of patient-reported symptoms showed similar differences between vaginal brachytherapy and EBRT, with 5.6% versus 22.7% of patients reporting moderate to severe diarrhoea.[12, 30] Long-term analysis of the PORTEC-2 showed that only 1.8% and 0.9% of patients treated with vaginal brachytherapy had persistent moderate to severe symptoms of faecal leakage and diarrhoea, respectively, versus 10.6% and 8.4% after EBRT. Genito- urinary symptoms as vaginal dryness, narrowing, or pain did not differ significantly between vaginal brachytherapy and EBRT.[29]

Figure 2. Vaginal brachytherapy dose distribution and organs-at risk.



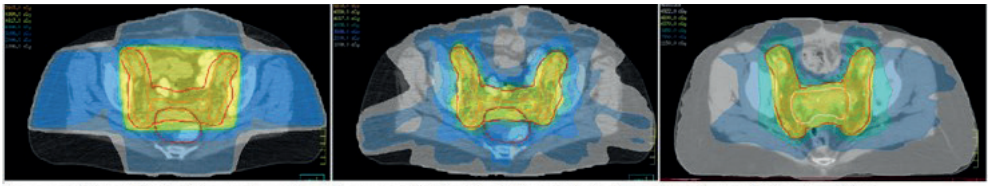
Single channel cylinder for vaginal brachytherapy with the 100% isodose line being 7Gy (red) covering the proximal 4 cm of the vaginal mucosa. Organs-at-risk are contoured: bladder (blue), rectum (red), sigmoid (brown) and small bowel (yellow).

External beam radiotherapy

Over the past 10 to 20 years, radiotherapy techniques have developed from 2-dimensionally planned radiotherapy to three and four field techniques, and three-dimensional (3D) conformal radiotherapy. Most recent developments are 3D image-guided intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc radiotherapy (VMAT) (*Figure 3*). With IMRT and VMAT, the radiation dose is delivered more conformally to the target volume and the dose to the adjacent organs at risk is reduced, compared to 3D conformal radiotherapy, without compromising clinical outcome.[45-50] With the introduction of more advanced radiotherapy techniques, it is expected that treatment related toxicity for pelvic radiotherapy can be reduced. Multiple retrospective studies and two prospective randomised trials have shown that intensity modulated techniques significantly reduce treatment related acute and late adverse events and patient-reported symptoms in women with endometrial or cervical cancer.[49-57]

Analyses of acute toxicity showed that pelvic radiotherapy was associated with mostly gastro-intestinal acute toxicity of mild to moderate severity, and that the addition of chemotherapy resulted in added hematological and neurological toxicity.[39, 40] Within the PORTEC-3 trial, 68.5% (94.2% chemoradiation vs 43.2% radiotherapy alone) had any grade $\geq$ 2 toxicity during treatment, and 44.3% and 43.8% of all patients experienced grade $\geq$ 2 gastro-intestinal and hematological toxicity, respectively. Persistent grade $\geq$ 2 toxicity, up to 5 years after treatment, were observed for 31.0%, with 7.3% gastro-intestinal and 2.5% hematological toxicity. Long-term grade 3 to 4 toxicity was observed in 3-6.8% of patients in the PORTEC-1 and 3 trials.[58, 59]

Figure 3. External beam radiotherapy techniques over time.



Improved dose distribution and sparing of organs at risk with different techniques over the past decades (from left to right): 3D-conformal radiotherapy (left), intensity-modulated radiotherapy (IMRT)(middle) and volumetric-arc radiotherapy (VMAT)(right), showing increased conformality of the radiotherapy plans.

1.7 Molecular risk factors

In 2013 the Cancer Genome Atlas Group (TCGA) analysed the molecular genetic basis of endometrial cancer development, which has been pivotal in understanding the molecular pathways involved in endometrial cancer development and their prognostic implications. By comprehensive genomic analysis of 373 endometrial cancer cases, 4 different molecular subclasses were identified based on mutation rates and somatic copy number alterations (SCNA). The ultra-mutated subclass, characterised by mutations in the exonuclease domain of DNA polymerase-epsilon (*POLE)*, is associated with a very favourable prognosis. The hypermutated subclass based on microsatellite instability (MSI) has been shown to have an intermediate prognosis. The copy number low subclass with low mutation frequency (also called subclass with no specific molecular profile or NSMP), has also been associated with an (stage dependent) intermediate prognosis. The copy number high subclass, characterised by *TP53* mutations, with mainly serous type endometrial cancer has a very high degree of SCNAs and a low mutation rate, and is associated with the most unfavourable prognosis.[60] Several research groups have reproduced and validated the four TCGA subclasses in formalin-fixed, paraffin-embedded tissues in different endometrial cancer cohorts by using their surrogate markers. These findings have led to a clinically available molecular classification tool for diagnosis and decision making and is implemented more and more into the risk classification and treatment guidelines, such as the recent ESGO-ESTRO-ESP endometrial cancer guidelines.[61-66] The value of incorporating molecular classification in clinical decision making for adjuvant treatment is currently being investigated in the randomised PORTEC-4a trial for women with high-intermediate risk endometrial cancer. In this trial, women are randomised 1:2 to either the standard brachytherapy arm versus an experimental arm in which women are stratified in a favourable, intermediate or unfavourable profile based on molecular and clinicopathologic risk factors and consequently treated with no adjuvant treatment, vaginal brachytherapy or EBRT, respectively.[67]

1.8 Aims and outline of this thesis

The aims of this thesis are to evaluate the role of radiotherapy for women with endometrial cancer, and the impact molecular factors have on assignment of adjuvant treatment. In the Netherlands, the current standard adjuvant treatment for high-intermediate risk endometrial cancer is vaginal brachytherapy, which is based on the outcomes of the PORTEC-2 trial. The PORTEC-2 trial investigated the efficacy of external beam radiotherapy versus vaginal brachytherapy for women with high-intermediate risk endometrial cancer.

The long-term outcomes of the PORTEC-2 trial, including the evaluation of clinicopathologic and molecular risk factors are described in **chapter 2**. Whether these molecular risk factors could be implemented into the current treatment guidelines is currently investigated in the PORTEC-4a trial. Evaluation of the pilot phase of the trial is described in **chapter 3**. As approximately 60% of women in the PORTEC-4a trial are treated with vaginal brachytherapy, a quality assurance programme, to verify protocol adherence, was implemented in the trial. The results are evaluated in **chapter 4**.

For women with high-risk endometrial cancer the current standard adjuvant treatment is pelvic EBRT with or without chemotherapy. The PORTEC-3 trial investigated radiotherapy versus radiotherapy combined with chemotherapy for women with high-risk endometrial cancer. Before participating in the PORTEC-3 trial, upfront pathology review was performed to ensure a truly high-risk trial population. Results of the upfront pathology review are described in **chapter 5**. Within the PORTEC-3 trial women were treated with pelvic external beam radiotherapy, which has developed from 3D-conformal towards more conformal intensity-modulated radiotherapy techniques as IMRT and VMAT over the past 10-20 years. In **chapter 6** the effect of both techniques on toxicity and quality of life is evaluated. **Chapter 7** provides a general discussion.

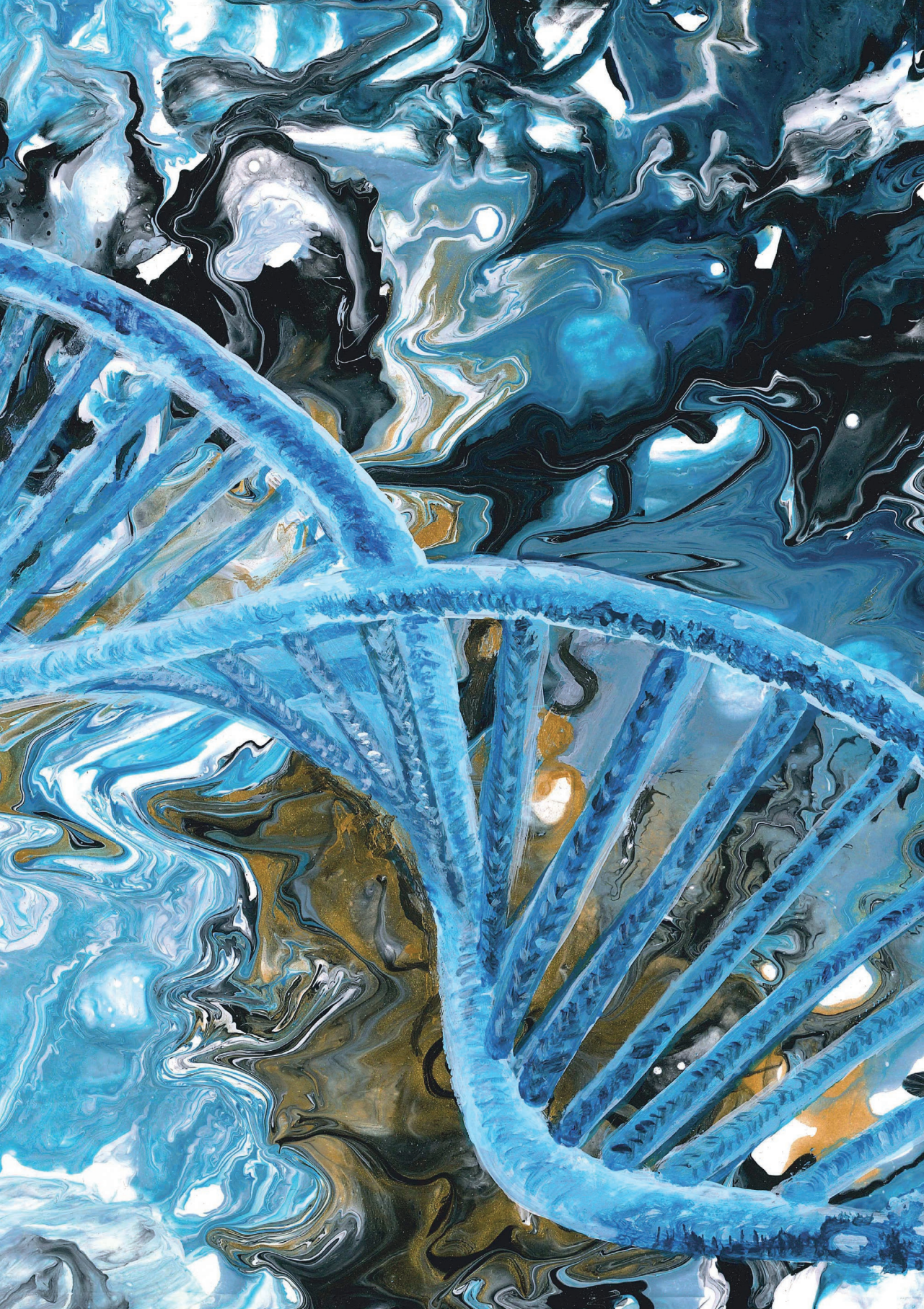
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CHAPTER 2

TEN-YEAR RESULTS OF THE PORTEC-2 TRIAL FOR HIGH-INTERMEDIATE RISK ENDOMETRIAL CARCINOMA: IMPROVING PATIENT SELECTION FOR ADJUVANT THERAPY

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ABSTRACT

Background: PORTEC-2 was a randomised trial for women with high-intermediate risk (HIR) endometrial cancer, comparing pelvic external beam radiotherapy (EBRT) with vaginal brachytherapy (VBT). We evaluated long-term outcomes combined with the results of pathology review and molecular analysis.

Methods: 427 women with HIR endometrial cancer were randomised between 2002-2006 to VBT or EBRT. Primary endpoint was vaginal recurrence (VR). Pathology review was done in 97.4%, combined with molecular analysis.

Results: Median follow-up was 116 months; 10-year VR was 3.4% versus 2.4% for VBT vs EBRT (p=0.55). Ten-year pelvic recurrence (PR) was more frequent in the VBT group (6.3% vs. 0.9%, p=0.004), mostly combined with distant metastases (DM). Ten-year isolated PR was 2.5% vs. 0.5%, p=0.10, and DM 10.4 vs 8.9% (p=0.45). Overall survival for VBT vs EBRT was 69.5% vs 67.6% at 10-years (p=0.72). L1CAM and p53-mutant expression and substantial lymph-vascular space invasion were risk factors for PR and DM. EBRT reduced PR in cases with these risk factors.

Conclusion: Long-term results of the PORTEC-2 trial confirm VBT as standard adjuvant treatment for HIR endometrial cancer. Molecular risk assessment has the potential to guide adjuvant therapy. EBRT provided better pelvic control in patients with unfavourable risk factors.

INTRODUCTION

Women with endometrial cancer (EC) are often diagnosed at early stage of disease, and in general have a favourable prognosis.[1] Randomised trials have shown that adjuvant radiation therapy (RT) for stage I EC significantly reduced the risk of locoregional recurrence, without difference in overall survival.[2-5] High-intermediate risk (HIR) factors were defined in both the PORTEC-1 and GOG#99 trials to identify women who were at relatively higher risk of recurrence.[2, 4] As the majority of recurrences in these trials were located in the vaginal vault, the Post-Operative Radiation Therapy in Endometrial Cancer trial (PORTEC)-2 trial was initiated in 2002 to investigate the efficacy of vaginal brachytherapy (VBT) as compared to pelvic RT (EBRT) for women with stage I EC with HIR factors to maximise local control, with reduced toxicity and better quality of life. Five-year results of the PORTEC-2 trial showed equally low rates of vaginal recurrence in both treatment arms, without differences in overall and disease-free survival.[6] Higher rates of treatment-related toxicity, especially gastro-intestinal symptoms with impact on health-related quality of life (HRQL), were recorded in the EBRT arm, while patients who received VBT reported HRQL and symptoms scores which did not differ from those of an age-matched norm population.[7-9] As a result, VBT became standard adjuvant treatment for women with HIR endometrial carcinoma.

More recently, novel molecular risk factors in endometrial cancer were described. In 2013 the Cancer Genome Atlas (TCGA) group published results of an extensive genomic characterisation of endometrial cancer, defining four different molecular subgroups with distinct prognosis: a *POLE*-ultramutated group; a microsatellite-unstable hypermutated group; a copy-number-low group and a copy-number-high group driven by *TP53* mutation.[10] *POLE*-ultramutated EC had very favourable outcomes, while those with *TP53* mutation had an unfavourable prognosis. For the copy-number-low group, no specific driver mutation was identified. Analysis of these four molecular subgroups by their surrogate markers (p53 expression by immunohistochemistry; PCR based determination of microsatellite instability (MSI); and analysis of POLE exonuclease domain mutations by Sanger sequencing) in more than 900 paraffin-embedded (FFPE) tissue samples of the PORTEC-1 and PORTEC-2 biobank, led to a useful and practical molecular classification tool for the clinic. Results of these analyses confirmed the prognostic significance of these 4 molecular subgroups, which was confirmed in a similar analysis reported by Talhouk et al.[11, 12] Moreover, several other strong clinicopathologic and molecular risk factors such as substantial (diffuse or multifocal) lymph- vascular space invasion (LVSI), L1CAM expression and beta catenin mutation were analysed. A molecular integrated risk profile was defined which was able to distinguish favourable, intermediate and unfavourable subgroups within the group of HIR EC, with a clear difference in outcomes.[11-14]

With current knowledge of molecular risk features, the question remains whether patient selection for vaginal brachytherapy can be further improved, thereby decreasing both over- and undertreatment. It was hypothesised that a small subgroup of patients with unfavourable risk features such as *TP53* mutation, L1CAM expression (>10%), or substantial LVSI might have had better pelvic control if they had received EBRT. The present analysis was done to analyse long-term outcomes of the PORTEC-2 trial, and evaluate whether specific clinicopathologic and molecular risk factors can be used to determine optimal adjuvant treatment for subgroups at higher risk of recurrence.

METHODS

Patient selection and eligibility criteria

The PORTEC-2 trial was a multicentre randomised trial, which recruited patients between May 2002 and September 2006. Women were eligible if they had been diagnosed with endometrial carcinoma with high-intermediate risk factors (HIR) and were randomly allocated to either vaginal brachytherapy (VBT) or pelvic radiotherapy (EBRT). HIR was defined as either (1) FIGO 1988 stage 1C (≥50% myometrial invasion) with age greater than 60 and grade 1 or 2; or (2) FIGO 1988 stage 1B (<50% myometrial invasion) with age greater than 60 and grade 3; or (3) FIGO 1988 stage 2A (endocervical glandular involvement, which is stage I in FIGO 2009) with any age, except for grade 3 with deep invasion. Exclusion criteria were: serous or clear cell carcinoma; staging lymphadenectomy; >8 weeks interval between surgery and radiotherapy; history of previous malignancy; previous radiotherapy, hormonal or chemotherapy; Crohn's disease or ulcerative colitis. Detailed information on patient selection, randomisation and masking, treatment and follow-up was described previously.[6] The primary endpoint of the study was vaginal recurrence (VR). Secondary endpoints were pelvic recurrence (PR), distant recurrence (DR), overall survival, endometrial cancer-related survival (CSS), disease-free survival (DFS), and toxicity and quality of life. The trial protocol was approved by the Dutch Cancer Society (CKTO 2001–04) and the Ethics Committees of participating centres. Written informed consent was given by all patients.

Treatment and follow-up

Radiation therapy was administered within 8 weeks after total abdominal hysterectomy and bilateral salpingo-oophorectomy. Lymphadenectomy was not performed routinely.[15, 16] In case of suspicious lymph nodes found at surgery, these were selectively removed. EBRT was delivered to the pelvic area using a total dose of 46 Gy in 2 Gy daily fractions, five times per week. The clinical target volume consisted of the proximal vagina parametria, and internal, external and caudal common iliac lymph node regions up to the level of the promontory. Treatment planning

was performed by CT-based three-dimensional conformal planning using multiple fields with individual shielding; usually a 4-field box technique.

VBT was delivered with a vaginal cylinder to the proximal half of the vagina, with dose specification at 5mm distance from the surface of the cylinder. High-dose rate (HDR) equipment was used in 85%, delivering a dose of 21 Gy in 3 fractions of 7 Gy, with an interval of 1 week; 15% received an equivalent dose using LDR (0.5-0.7 Gy/hr) or MDR (1 Gy/hr) equipment.[6]

Follow-up consisted of alternating visits to the patient's gynaecologist and radiation oncologist every 3-4 months in the first 3 years, at 6 month intervals in the 4th and 5th years, and yearly thereafter, up to at least 7 years. If needed, follow-up information was obtained from the GP and the national population registry at 10 years after treatment. At follow-up visits, physical examination was performed and side-effects or recurrence of disease were reported and treated. Patient-reported health-related quality of life and symptoms were recorded by the EORTC QLQ-C30 and specific symptom modules for bladder, bowel and sexual symptoms. Short-term and long-term quality of life outcomes have been reported separately.[7-9]

Pathology review and analysis of molecular characteristics

Central pathology review was performed by specialised gynaeco-pathologists, after the patient had been included in the trial. More recently, comprehensive analysis of molecular alterations has been done, in a translational research project using the pooled PORTEC-1 and PORTEC-2 biobank.[11] TCGA molecular subgroups were assessed using surrogate markers on FFPE tissue samples.[11,12] Immunohistochemical techniques and DNA analysis were used to assess polymerase-epsilon (*POLE*) mutations; microsatellite instability (MSI); and p53 protein expression (scored as p53-wildtype/mutant/null staining).[11] In addition, analysis of L1CAM expression, with >10% expression being L1CAM positive, and the presence and quantification of LVSI were assessed, according to the methods described previously.[13,14] Based on previous analyses, only substantial LVSI was taken into account, since mild (focal) LVSI was not associated with increased risk of recurrence.[14]

Statistical analysis

All randomised patients were kept in the analyses for primary and secondary endpoints, which was by intention to treat. Analysis of molecular risk factors was performed only in those patients whose high-intermediate risk features were confirmed at central pathology review (confirmed-HIR). For these analyses of confirmed-HIR cases, data of the previous study on the molecular risk factors within the PORTEC-1 and 2 biobank were used (selecting the PORTEC-2 cases only).[11]

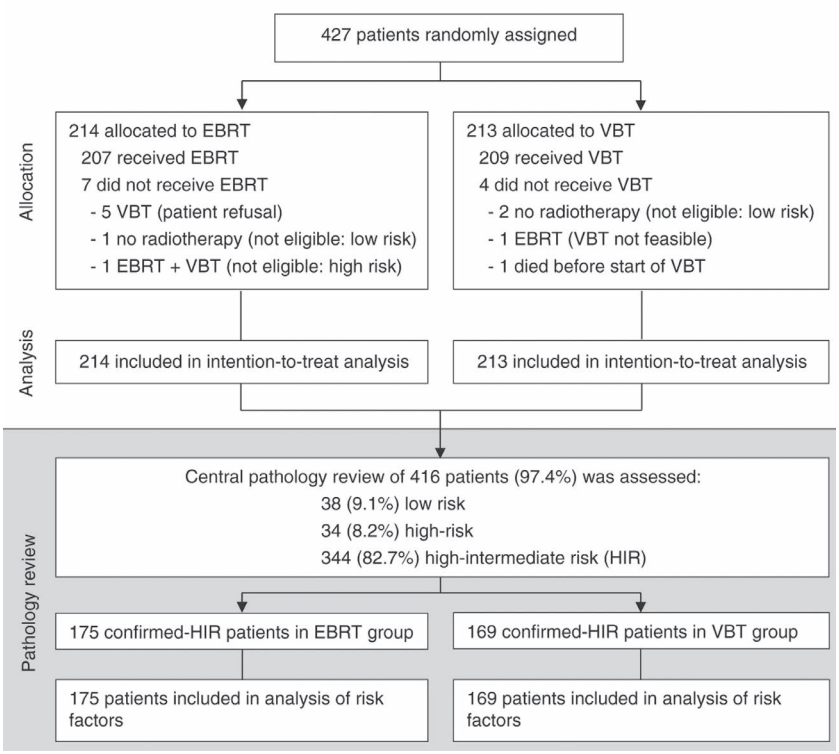
Time-to event analyses were done with log-rank tests and Cox proportional hazards regression models with date of randomisation as starting point. Both log-rank tests and Cox regression models were stratified for FIGO stage but were essentially the same with and without adjustment, and results are presented without adjustment. Overall survival (OS) was calculated from date of randomisation to death from any cause, with censoring at date of last information for patients alive. Endometrial cancer-related survival (CSS) was calculated from date of randomisation to date of death related to endometrial cancer, with censoring of patients who died of other causes and of patients alive at date of death or last information, respectively. Disease-free survival (DFS) was calculated from date of randomisation to date of disease recurrence or to date of death from any cause, with censoring of patients alive and recurrence-free. Data for patients who were alive and recurrence-free were censored at date of last follow-up or of information on vital status.

The competing risk method (with death as competing risk) was used for analysis of vaginal, and pelvic recurrence and distant metastasis. First failure type was vaginal recurrence when an isolated vaginal recurrence had occurred; pelvic recurrence in case of pelvic recurrence with or without vaginal recurrence; and first failure type was distant if a distant recurrence was diagnosed, with or without pelvic or vaginal recurrence. The Kaplan-Meier method was used for OS, CSS and DFS. Analyses of (molecular) risk factors were done using univariable Cox proportional hazard models.[11] Risk factors with a p-value below 0.1 in univariable analysis were included in multivariable analysis. Chi-square and Fisher's exact tests were used to compare (molecular) risk factors between treatment groups. SPSS was used to perform statistical analyses, version 23.0 (IBM SPSS, Inc., Chicago, IL).

RESULTS

In total, 427 women with HIR endometrial carcinoma were included in the trial; 214 were randomly assigned to receive EBRT and 213 to VBT (Figure 1). Patient and tumour characteristics were equally distributed over the two treatment groups (Table 1). The database was frozen on May 1st 2016 and by then, the median follow-up was 116 months (range 18 – 163 months).

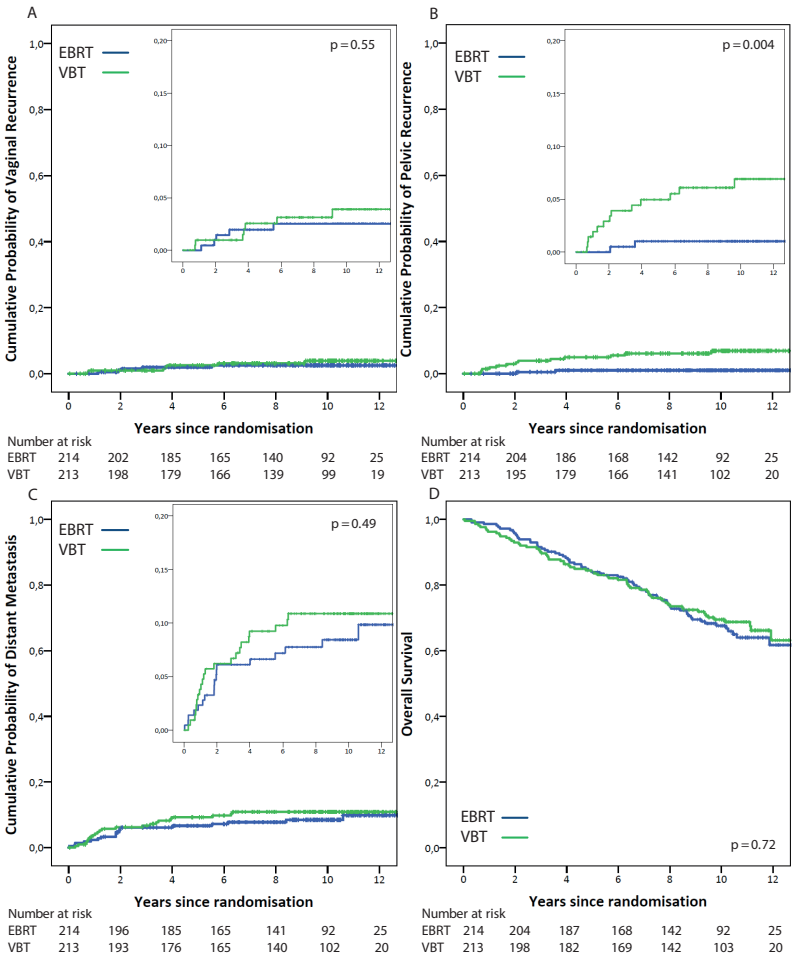
Figure 1. Consort diagram of the PORTEC-2 trial with pathology review.



EBRT = External beam radiotherapy. VBT = Vaginal brachytherapy.

Long-term results of the intention to treat analysis are presented in Table 2 and Figure 2. A total of 12 women developed a vaginal recurrence, 7 in the VBT group and 5 in the EBRT group. The 10-year vaginal recurrence rates were 3.4% and 2.4% for VBT and EBRT, respectively (p=0.55). Pelvic recurrences were diagnosed in 13 women in the VBT group and 2 in the EBRT group, with 10-year rates of 6.3% vs 0.9% (p=0.004); of these, 2.5% vs 0.5% were isolated pelvic recurrences (p=0.10). Ten-year rates of distant metastases were 10.4% vs 8.9% for VBT vs EBRT (p=0.45). No significant differences in first failure types were found, except for simultaneous distant and pelvic recurrence: 3.6% in the VBT group versus 0.5% in the EBRT group, p=0.03. Long-term results of the confirmed-HIR population are shown in the Supplementary Data Table 2. In this population the 10-year vaginal recurrence rates were 2.7% vs 3.1% (p=0.78) and the pelvic recurrence rates 7.4% and 1.2% (p=0.01) for VBT vs EBRT, respectively.

Figure 2. Ten year results. Cumulative probability of vaginal recurrence (A), pelvic recurrence (B), distant metastasis (C) and overall survival (D).



EBRT = External beam radiotherapy. VBT = Vaginal brachytherapy.

A total of 136 women died during follow-up: 70 in the VBT group and 66 in the EBRT group. Cause of death was endometrial carcinoma in 30.1%; secondary cancer in 13.2%; and intercurrent disease in 50.7%. Ten-year overall survival was 69.5% vs 67.6% (p=0.72) and 10- year endometrial cancer-related survival 88.2% vs 90.9% (p=0.42) for VBT vs EBRT groups, respectively.

Prognostic factors

Central pathology review was available for 416 patients (97.4%). HIR status was confirmed by the review gynaeco-pathologist in 344 cases (82.7%), while 34 were determined high risk (8.2%) and 38 low risk (9.1%), see Table 1 and Figure 1. Figure 3A shows the CSS for the four molecular subgroups in confirmed

HIR patients. For women with tumours harbouring a *POLE* mutation, 10-year CSS was 100%, in contrast to 96.2% for no specific molecular profile, 84.8% for MSI and 62.3% for p53-mutant tumours ($p<0.001$).

Among confirmed HIR patients a subgroup of 50 women presented with any of the unfavourable risk features substantial LVSI, p53-mutant and/or L1CAM expression; 17.2% in the VBT group and 12% in the EBRT group, p=0.18. L1CAM expression was found in 14 VBT patients, versus 4 in the EBRT arm (p=0.010). Rates of substantial LVSI and p53-mutant expression did not differ significantly between the treatment arms, see Table 1. Eleven patients had both p53–mutant and L1CAM expression, and 3 had both LVSI and L1CAM expression.

Table 1. Patient and tumour characteristics and pathology review.

Intention to treat population				
N = 427	**EBRT (N=214)**		**VBT (N=213)**	
Age				
</= 60 years	8	3.7%	8	3.8%
60-70 years	109	50.9%	99	46.5%
> 70 years	97	45.3%	106	49.8%
FIGO 1988 stage				
IB	19	8.9%	16	7.5%
IC	172	80.4%	171	80.3%
IIA	23	10.7%	26	12.2%
Myometrial invasion				
< 50%	31	14.5%	28	13.1%
> 50%	183	85.5%	185	86.9%
Grade				
1	99	46.3%	103	48.4%
2	97	45.3%	94	44.1%
3	18	8.4%	16	7.5%
LVSI				
Present	25	11.7%	21	9.9%
Absent	189	88.3%	192	90.1%
Confirmed-HIR at pathology review				
N = 344	**EBRT (N=175)**		**VBT (N=169)**	
Grade				
1	148	84.6%	134	79.3%
2	16	9.1%	23	13.6%
3	11	6.3%	12	7.1%
Substantial LVSI				
Yes	9	5.1%	7	4.1%
No	160	91.4%	156	92.3%
Missing[1]	6	3.4%	6	3.6%
Molecular subgroup				
POLE	10	5.7%	6	3.6%
MSI	41	23.4%	36	21.3%
NSMP	103	58.9%	96	56.8%
TP53[2]	10	5.7%	15	8.9%
Double classifiers	4	2.3%	6	3.6%
Missing[1]	7	4.0%	10	5.9%
L1CAM expression[3]				
>10%	4	2.3%	14	8.3%
<10%	168	96.0%	151	89.3%
Missing[1]	3	1.7%	4	2.4%

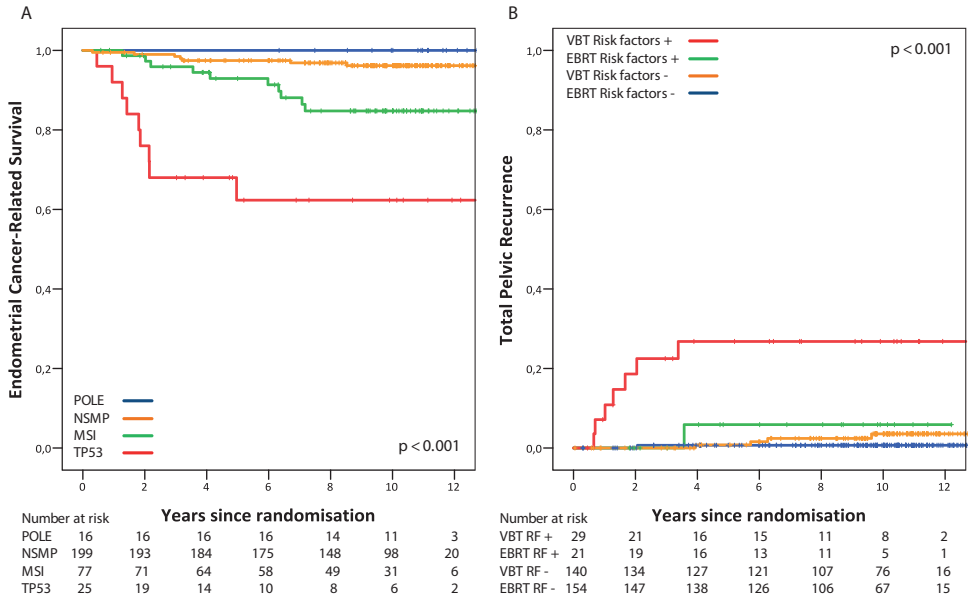
[1] Material not appropriate for test or failed test
[2] As assessed by p53 protein expression
[3] Significant difference (p = 0.010)

Table 2. Long-term outcomes (intention to treat population).

	EBRT (N=214)			VBT (N=213)			HR (95% CI)	
	Events	5-year %	10-year %	Events	5-year %	10-year %	VBT:EBRT	p-value
First failure type								
Vaginal recurrence	3	1.1%	1.5%	5	0.9%	3.0%	1.68 (0.40 - 7.03)	0.47
Pelvic recurrence	1	0.5%	0.5%	5	1.4%	2.5%	5.07 (0.59 - 43.41)	0.10
Distant recurrence	18	6.6%	8.9%	22	8.9%	10.4%	1.25 (0.67 - 2.33)	0.49
distant alone	15	5.7%	7.0%	13	5.5%	6.6%	0.88 (0.42 - 1.86)	0.75
distant and pelvic	1	0.5%	0.5%	7	3.0%	3.6%	7.16 (0.88 - 58.23)	0.03
distant and vaginal	2	0.5%	1.1%	1	0.5%	0.5%	0.51 (0.05 - 5.65)	0.58
Total failures								
Vaginal recurrence	5	1.9%	2.4%	7	2.4%	3.4%	1.42 (0.45 - 4.46)	0.55
Pelvic recurrence	2	0.9%	0.9%	13	4.6%	6.3%	6.65 (1.50 - 29.48)	0.004
Distant recurrence	18	6.6%	8.9%	22	8.9%	10.4%	1.25 (0.67 - 2.33)	0.49
Endometrial cancer-related survival	18	93.2%	90.9%	23	91.7%	88.2%	1.29 (0.70 - 2.39)	0.42
Disease-free survival	71	82.1%	68.0%	72	81.2%	66.7%	1.03 (0.74 - 1.43)	0.87
Overall survival	70	84.0%	67.6%	66	84.0%	69.5%	0.94 (0.67 - 1.32)	0.72

Multivariable analysis of unfavourable risk factors in confirmed HIR patients is presented in Table 3 and similar results were found in all patients with material available (Supplementary Data Table 1). Substantial LVSI was found to be a very strong independent risk factor for pelvic and distant recurrence (hazard ratios 8.73 (p=0.005) and 5.36 (p=0.001), respectively) and for endometrial cancer-related survival (HR 7.16, p<0.001). L1CAM expression (HR 4.18, p=0.016) and p53-mutant expression (HR 3.35, p=0.015) were significant prognostic factors for distant recurrence and CSS (HR 5.05, p=0.006 and HR 3.30, p=0.015). Main findings of multivariable analysis for DFS were similar to those of CSS (data not shown). Although significant in univariable analysis, L1CAM and p53-mutant expression did not reach significance for pelvic recurrence in multivariable analysis. Figure 3B and Supplementary Data Figure 1 show that the higher risk of total pelvic recurrence in the VBT group is restricted to patients with unfavourable features.

Figure 3. Endometrial cancer-related survival by 4 molecular subgroups **(A)**. Total pelvic recurrence by unfavourable risk factors (LVSI, p53-mutant or L1CAM overexpression) **(B)**.



VBT = vaginal brachytherapy. EBRT = external beam radiotherapy. LVSI = Lymph-vascular space invasion. MSI = microsatellite instability. NSMP = no specific molecular profile. RF = risk factors.

Table 3. Multivariable analysis of recurrence in confirmed-HIR patients.

		Pelvic recurrence (total)		Distant recurrence		Endometrial cancer-related survival	
	No. [1]	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Treatment group							
EBRT	163	1	0.054	1	0.805	1	0.740
VBT	154	4.58 (0.97 - 21.52)		0.91 (0.41 - 2.00)		0.87 (0.40 - 1.94)	
LVSI							
no/mild	301	1	0.005	1	0.001	1	< 0.001
substantial	16	8.73 (1.95 - 39.22)		5.36 (1.91 - 15.07)		7.16 (2.71 - 18.91)	
TP53[2]							
wild type	288	1	0.065	1	0.015	1	0.015
mutation	29	3.82 (0.92 - 15.83)		3.35 (1.27 - 8.84)		3.30 (1.26 - 8.64)	
L1CAM							
< 10%	300	1	0.126	1	0.016	1	0.006
> 10%	17	3.79 (0.69 - 20.93)		4.18 (1.31 - 13.33)		5.05 (1.59 - 16.06)	

[1] Total no 317; 27 cases had insufficient material for analysis of all factors.

[2] As assessed by p53 protein expression

DISCUSSION

The present analysis of long-term results of the PORTEC-2 trial confirmed the excellent vaginal control with adjuvant vaginal brachytherapy for women with high-intermediate risk endometrial cancer, with 10-year vaginal control above 96% in both arms. Although the risk of pelvic recurrence was significantly (6% vs 1%) higher in the VBT group, the majority of these women presented with simultaneous distant metastasis, resulting in similarly low rates of isolated pelvic recurrence in both treatment arms. Moreover, no differences were found in 10-year rates of distant metastasis and overall survival. As previously reported, low toxicity rates and better health-related quality of life were found among women who received VBT compared to EBRT, even after more than 7 years.[9] Similar findings were reported in a Swedish trial comparing EBRT combined with VBT versus VBT alone for women with intermediate-risk endometrial cancer.[17] The 5-year locoregional relapse rates were 1.5% versus 5% (p=0.013), with crude rates of vaginal recurrence of 1.9% versus 2.7%, and quality of life results favoured VBT. These long-term findings confirm VBT as the adjuvant treatment of choice for women with early stage endometrial cancer with high-intermediate risk features.

Implementation of HIR risk factors as determined in both the PORTEC-1 and GOG#99 trials for the indication for adjuvant radiotherapy reduced the number of women who received radiotherapy by 50% at the time, sparing them unnecessary and potentially toxic treatment.[2-4, 18] In the PORTEC-1 trial, the 5-year risk of vaginal recurrence among women with high-intermediate risk features was reduced from 15% without radiotherapy, to 2% with EBRT. Although the risk of vaginal recurrence was subsequently found in the PORTEC-2 trial to be similarly low with VBT, it can be argued that this still represents overtreatment, as 8 women need to be treated to prevent 1 vaginal recurrence, and selection for adjuvant treatment could be improved.[19] Moreover, EBRT might have provided better pelvic control for the few (6%) patients who developed pelvic recurrence after VBT, even if the majority presented with simultaneous distant metastases. These results indicate there is a clear need for additional risk factors that improve the current risk classification.

Both the TCGA analysis and studies determining the molecular subgroups by their surrogate markers indicated that distinguishing the 4 molecular subgroups had strong prognostic significance.[10-12] Mutation of the tumour suppressor gene *TP53* has been related to early tumour progression in multiple cancer types as well as in endometrial cancer, and is associated with grade 3 and with non-endometrial (mostly serous) histology, while *POLE* mutation leads to only rare recurrence and excellent outcomes.[20] MSI is an intermediate risk factor but associated with Lynch syndrome and might have therapeutic implications. More recently MSI detection has been replaced by analysis of mismatch repair deficiency (MMRd), and detection of MLH-1 promotor hypermethylation in those with MMRd.[21] Substantial LVSI and L1CAM expression are strong risk

factors for recurrence.[10, 11, 13, 14] L1CAM is a cell adhesion molecule and mediates cell motility, is associated with epithelial mesenchymal transition and early disease spread. Several large series have confirmed the negative prognostic impact of L1CAM expression.[13, 22, 23] Interestingly, while there is some overlap between *TP53* mutation and L1CAM expression, L1CAM has been shown to be an independent risk factor, frequently associated with, but independent from *TP53* mutation.[24] This was confirmed in the current analysis, where 38% of L1CAM positive patients did not have p53-mutant expression, and 63% of patients with p53-mutant expression did not have L1CAM expression. LVSI has long been known for its adverse prognostic impact, being associated with the risk of (microscopic) nodal metastases and with higher rates of recurrence and lower CSS, both in the presence and absence of lymph node metastases.[25, 26] A recent large study using the pooled PORTEC biobank in which LVSI was quantified and graded as absent, mild (a single focus or few foci) or substantial (diffuse or multifocal) showed that substantial LVSI is a highly significant risk factor for pelvic and distant recurrence.[14]

In this long-term analysis, substantial LVSI, p53-mutant and L1CAM expression were all strongly associated with the risk of pelvic recurrence, distant metastasis and endometrial cancer-related survival. Moreover, in the small subgroup of women with high-intermediate risk endometrial cancer with any of these unfavourable risk factors, EBRT provided a significantly better pelvic control than VBT.

Strengths of this study are the uniform and random allocation of treatment, long and complete follow-up and central pathology review in 97% of patients. Central pathology review was performed because various studies had shown frequent inter-observer variation within the field of gynaecopathology, with a poor reproducibility especially of the intermediate grade.[27-29] More recent analysis of the inter-observer variability in the pathology review of the PORTEC-3 trial, which was required before randomisation, showed that in 43% of all patients at least one of the pathology items changed, with grade (20%) and histological type (15%) being the most frequent items of disagreement. Upfront pathology review resulted in 8% of all patients being ineligible for the trial.[30]

Analysis of the long-term results within the population that was confirmed-HIR after pathology review in the PORTEC-2 trial (>80%) showed no significant differences compared to the intention to treat analysis, possibly also because a similar number of patients were deemed either low (38) or high risk (34) at pathology review (Figure 1, Supplementary Data Table 2).

These long-term results show that among the large group of women with early stage endometrial cancer with risk features, the subgroup of patients with unfavourable risk factors is small, and that the combination of clinicopathologic and molecular factors adequately select the women who might benefit from EBRT or more intensive treatment. This is supported by the fact that

more pelvic recurrences occurred in the VBT group, in which more patients with p53-mutant expression and with L1CAM expression were found compared to the EBRT group (Table 1).

The potential benefit of adjuvant chemotherapy to decrease disease recurrence in women with early stage, high-intermediate or high-risk endometrial cancer has been subject of several trials, which did not show differences in overall and relapse-free survival compared to EBRT.[31, 32] In the GOG249 trial, 601 women with stage I-II endometrial cancer with risk factors (deep invasion, grade 3 or serous/clear cell histology) were randomised to pelvic EBRT vs. VBT with 3 cycles of carboplatin/paclitaxel chemotherapy. Recently presented 5- year results showed no differences in relapse- free and overall survival.[33] However, even though 89% had lymphadenectomy and were node negative, pelvic and para-aortic failures were significantly more frequent after VBT and chemotherapy, while acute toxicity was increased, leading to the conclusion that EBRT remains the standard adjuvant treatment for early stage, high-risk disease. This finding again suggests that results of adjuvant EBRT are similar with and without lymphadenectomy, as was also seen in the GOG#99 and PORTEC-1 trial[2, 4], and that detecting microscopic nodal involvement, similar to extensive LVSI, seems a marker but not a cause of distant spread. Previous randomised trials have not shown any survival benefit from lymphadenectomy in early stage disease.[15, 16] The strength of the molecular markers is that they may more individually predict if specific tumours might be at risk of early disease spread. Therefore, an integrated clinicopathologic and molecular risk profile has the potential to guide adjuvant treatment and could distinguish the few women with HIR endometrial cancer who would benefit from EBRT instead of standard VBT.[11, 12] In the currently ongoing PORTEC-4a trial, women with stage I-II EC with high-intermediate risk features are randomised to receive adjuvant treatment directed by their integrated molecular risk profile or standard vaginal brachytherapy.[34] The molecular profile stratifies patients into favourable (about 50%) who will be observed, intermediate risk (about 45%) who will receive brachytherapy, and an unfavourable group (about 5%) who will receive EBRT, and thus aims to further refine risk stratification, reduce over- and undertreatment and increase cost-effectiveness. The PORTEC-4a trial was shown to be feasible by evaluation of the pilot phase, with a satisfactory patient acceptance rate and feasibility of performing the molecular assessment within 2 weeks.[35]

In conclusion, long-term results of PORTEC-2 confirmed VBT as the adjuvant treatment of choice for women with high-intermediate risk endometrial cancer. EBRT might provide better pelvic control in the small subgroup of women with unfavourable risk factors (substantial LVSI, L1CAM expression or p53-mutant expression).

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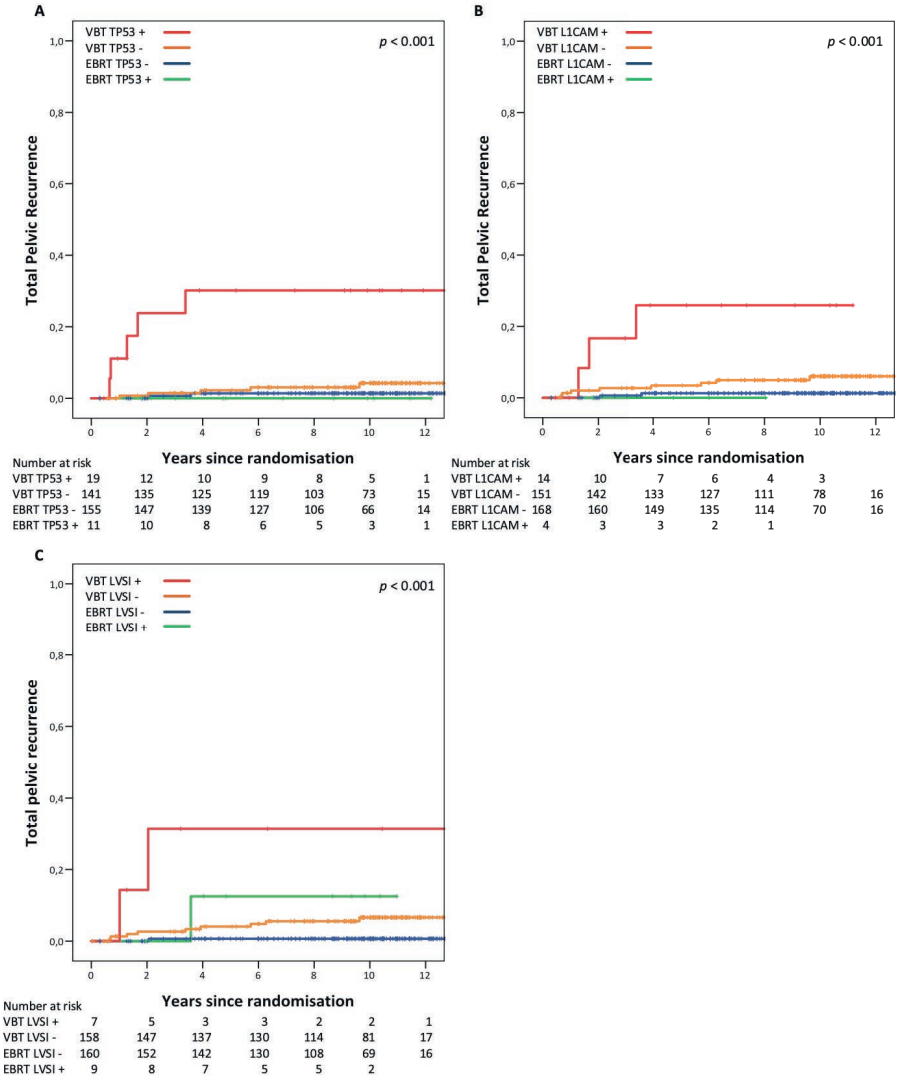
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SUPPLEMENTARY DATA

Supplementary Data Figure 1. Risk factors for pelvic recurrence. Total pelvic recurrence with p53-mutant expression (A), L1CAM (B). and substantial LVSI (C) by VBT and EBRT.



VBT = vaginal brachytherapy. EBRT = external beam radiotherapy. LVSI = Lymph-vascular space invasion. MSI = microsatellite instability. NSMP = no specific molecular profile.

Supplementary Data Table 1. Multivariable analysis of recurrence in patients with material available (no 416).

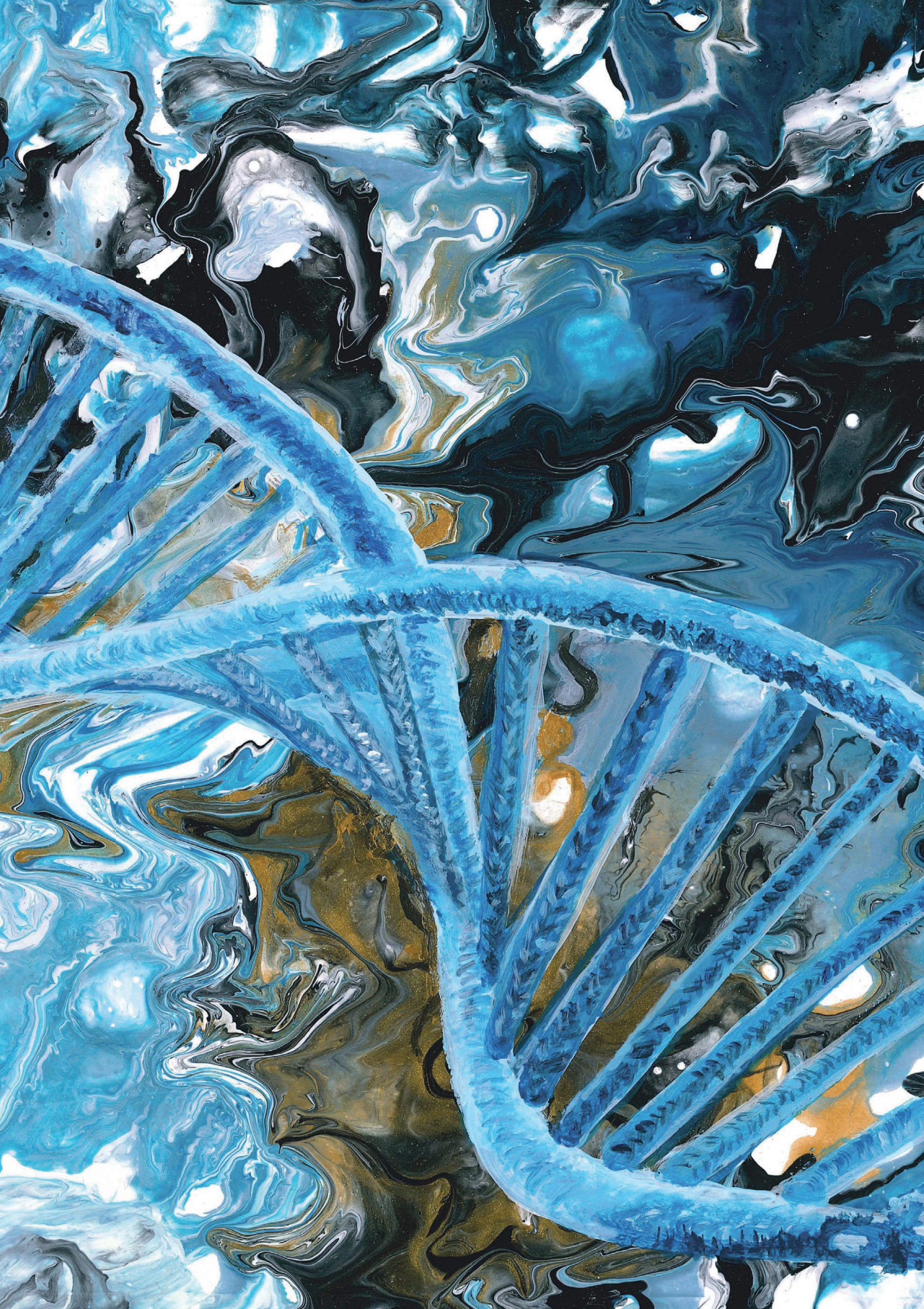
		Pelvic recurrence (total)		Distant recurrence		Endometrial cancer-related survival	
	No. [1]	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Treatment group							
EBRT	198	1	0.025	1	0.627	1	0.859
VBT	189	5.76 (1.25 - 26.54)		1.18 (0.61 - 2.28)		1.07 (0.54 -2.12)	
LVSI							
no/mild	367	1	0.005	1	< 0.001	1	< 0.001
substantial	20	10.08 (2.42 - 41.89)		6.31 (2.65 - 15.03)		6.94 (2.89 - 16.76)	
TP53[2]							
wild type	347	1	0.065	1	0.039	1	0.023
mutation	40	2.71 (0.73 - 10.12)		2.38 (1.05 - 5.41)		2.66 (1.15 - 6.17)	
L1CAM							
< 10%	355	1	0.126	1	0.002	1	0.001
> 10%	32	4.43 (1.01 - 19.34)		4.09 (1.71 - 9.75)		4.74 (1.94 - 11.61)	

[1] Total no 387; 29 cases had insufficient material for analysis of all factors

[2] As assessed by p53 protein expression

Supplementary Data Table 2. Long-term outcomes for the confirmed-HIR patients.

	EBRT (N=175)			VBT (N=169)			HR (95% CI)	
	Events	5-year %	10-year %	Events	5-year %	10-year %	VBT:EBRT	p-value
First failure type								
Vaginal recurrence	3	1.8%	1.8%	3	1.3%	2.1%	1.04 (0.21 - 5.13)	0.97
Pelvic recurrence	1	0.6%	0.6%	4	1.3%	3.0%	4.10 (0.46 - 36.74)	0.17
Distant recurrence	14	6.4%	8.6%	16	8.0%	10.0%	1.20 (0.58 - 2.45)	0.63
distant alone	11	5.2%	6.8%	8	3.7%	5.2%	0.76 (0.31 - 1.89)	0.55
distant and pelvic	1	0.6%	0.6%	7	3.8%	4.5%	7.38 (0.91 - 59.96)	0.03
distant and vaginal	2	0.6%	1.3%	1	0.6%	0.6%	0.53 (0.05 - 5.79)	0.59
Total failures								
Vaginal recurrence	5	2.4%	3.1%	4	1.9%	2.7%	0.83 (0.22 - 3.09)	0.78
Pelvic recurrence	2	1.2%	1.2%	11	5.0%	7.4%	5.77 (1.28 - 26.03)	0.01
Distant recurrence	14	6.4%	8.6%	16	8.0%	10.0%	1.20 (0.58 - 2.45)	0.63
Endometrial cancer-related survival	14	93.5%	91.4%	16	93.3%	89.7%	1.18 (0.57 - 2.41)	0.66
Disease-free survival	55	82.7%	68.3%	57	82.2%	67.6%	1.05 (0.72 - 1.52)	0.80
Overall survival	55	85.0%	67.8%	52	85.2%	70.4%	0.94 (0.64 - 1.37)	0.74



CHAPTER 3

MOLECULAR-INTEGRATED RISK PROFILE TO DETERMINE ADJUVANT RADIOTHERAPY IN ENDOMETRIAL CANCER: EVALUATION OF THE PILOT PHASE OF THE PORTEC-4A TRIAL

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Gynecologic Oncology (2018) 151:69-75

ABSTRACT

Objective: The Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-4a trial is a randomized trial for women with high-intermediate risk endometrial cancer (EC), comparing individualized adjuvant treatment based on a molecular-integrated risk profile to standard adjuvant treatment; vaginal brachytherapy. To evaluate patient acceptability and pathology logistics of determining the risk profile, a pilot phase was included in the study.

Methods: PORTEC-4a is ongoing and the first 50 patients enrolled were included in the pilot phase. Primary endpoints of the pilot phase were patient acceptance, evaluated by analyzing the screening logs of the participating centers, and logistical feasibility of determination of the risk profile within 2 weeks, evaluated by analyzing the pathology database.

Results: In the first year, 145 eligible women were informed about the trial at 13 centers, of whom 50 (35%) provided informed consent. Patient accrual ranged from 0-57% per center. Most common reasons for not participating were: not willing to participate in any trial (43.2%) and not willing to risk receiving no adjuvant treatment (32.6%). Analysis of the pathology database showed an average time between randomization and determination of the molecular-integrated risk profile of 10.2 days (1-23 days). In 5 of the 32 patients (15.6%), pathology review took more than 2 weeks.

Conclusions: The PORTEC-4a trial design was proven feasible with a satisfactory patient acceptance rate and an optimized workflow of the determination of the molecular- integrated risk profile. PORTEC-4a is the first randomized trial to investigate use of a molecular-integrated risk profile to determine adjuvant treatment in EC.

INTRODUCTION

Endometrial cancer (EC) is the most common gynecological cancer and primarily affects postmenopausal women between ages 60 and 80.[1] Primary treatment consists of surgery, most often laparoscopic hysterectomy and bilateral salpingo-oophorectomy.[2] The current indication for adjuvant radiotherapy depends on clinicopathological risk factors and has been investigated in several randomized trials.[3-6] In the PORTEC-1 and GOG 99 trials women with early stage EC were randomized to pelvic external beam radiotherapy (EBRT) or observation after surgery.[3,4] EBRT significantly reduced the risk of locoregional recurrence, without survival benefit. In the observation group, 75% of the locoregional recurrences were located in the vaginal vault. In the subsequent PORTEC-2 trial which included women with early stage EC with high-intermediate risk (HIR) factors, vaginal brachytherapy (VBT) was compared to EBRT. Results showed adjuvant VBT to be equally effective as EBRT for vaginal control (98% at 5 years in both arms), with less toxicity and improved quality of life.[6-8]

Based on the PORTEC-2 trial, adjuvant VBT became the standard of care for women with HIR EC. However, this may be overtreatment as 7-10 women need to be treated with VBT to prevent one recurrence.[9] An observational Danish population-based study showed that women with intermediate risk EC, who were observed after surgery, had similar survival rates but a higher risk of locoregional recurrence (14%) as compared to previous Danish data with use of radiotherapy.[10]

To prospectively investigate long-term local control and survival, the initial design of the PORTEC-4 study aimed to randomize women with HIR endometrial cancer 1:2 to observation or vaginal brachytherapy (VBT); subsequently, within the VBT arm, they were 1:1 allocated to standard dose VBT (21 Gy in 3 fractions) or reduced dose VBT (15 Gy in 3 fractions).[6] However, patient inclusion was difficult because the majority of eligible patients preferred treatment over observation. A patient preference study showed that patients preferred adjuvant VBT, which has limited toxicity and is highly effective, because of fear for recurrence of the disease and the more intensive salvage treatment in case of recurrence. Additionally, this study showed that even for a small local control benefit, radiation oncologists were likely to recommend VBT over observation.[11] For these reasons, the original PORTEC-4 trial design was not feasible, and new prognostic factors with impact on the risk of recurrence had emerged. After a major change in design, the trial continued as the PORTEC-4a trial as detailed below.

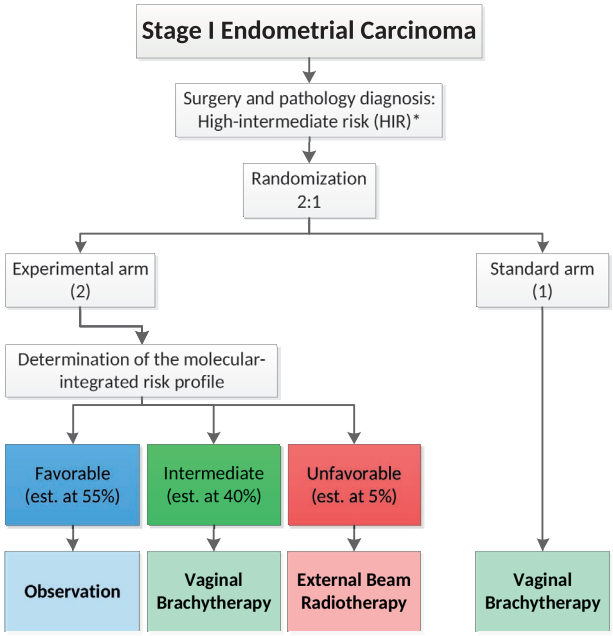
In 2013, the whole genome studies of the Cancer Genome Atlas (TCGA) analyzed the molecular genetic basis of EC development and defined four molecular subclasses, based on mutation burden and copy number alterations. The subclass with the highest mutational load were EC with mutations in the exonuclease domain of *DNA polymerase-epsilon (POLE),* associated with an

excellent prognosis. Microsatellite unstable EC (MSI, driven by mismatch repair deficiency) and the subclass copy number-low EC (also referred to as no specific molecular profile (NSMP)), had an intermediate outcome. The subclass characterized by high somatic copy number alterations, mostly driven by *TP53* mutation, were the most aggressive cancers with unfavorable prognosis.[12] Subsequently, in a comprehensive analysis of 947 EC from the pooled PORTEC-1 and PORTEC-2 biobank, it was shown that by use of surrogate markers for the TCGA subclasses their prognostic value could be confirmed.[13] Additionally, in this and other studies it was shown that L1 cell adhesion molecule (L1CAM) overexpression and substantial lymph-vascular space invasion (LVSI) were significant risk factors for both pelvic and distant recurrences. Within the NSMP group, ß-catenin (*CTNNB1)* was found to be prognostic for distant recurrence.[13-18] An integrated clinicopathologic and molecular risk profile was established for EC with HIR features, separating them in favorable, intermediate and unfavorable groups, each with a clearly different prognosis.[13]

To evaluate the clinical role of this molecular-integrated risk profile in the determination of adjuvant treatment in patients with HIR EC, the PORTEC-4a study was initiated in 2016. Women with HIR endometrial cancer are randomized (2:1) to the experimental arm, in which the molecular-integrated risk profile is determined and used to assign adjuvant treatment, or to standard VBT. Women with a favorable profile (*POLE* mutation, or NSMP without *CTNNB1* mutations) are observed after surgery; women with an intermediate risk profile (mismatch repair-deficient (MMRd) or NSMP with *CTNNB1* mutations) receive adjuvant VBT; and women with any of the unfavorable risk factors (substantial LVSI, *TP53* abnormal immunohistochemical staining or L1CAM overexpression) are treated with EBRT. See Figure 1A and 1B.

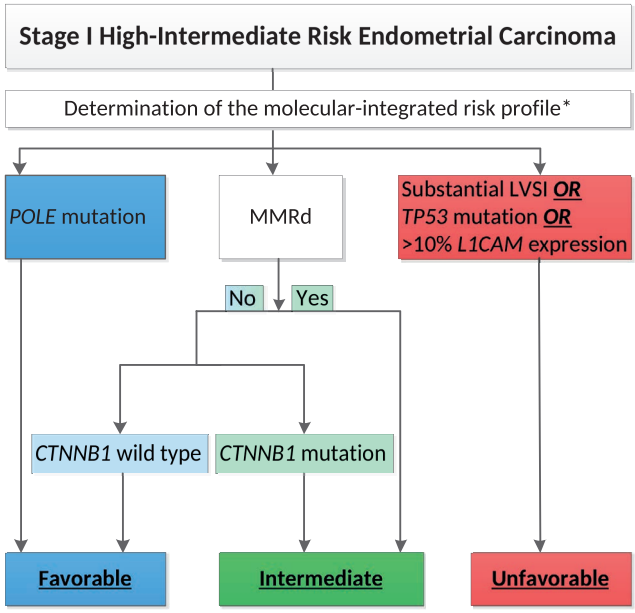
The PORTEC-4a trial was designed with an initial pilot phase of 50 patients. Objectives were to assess patient acceptance of the experimental arm and the logistical feasibility of determining the molecular-integrated risk profile within 2 weeks, as patients must start radiotherapy within a clinically acceptable time frame of 8 weeks from the date of surgery. Here we report on the results on the pilot phase of the PORTEC-4a trial.

Figure 1A. Study design of the PORTEC-4a trial.



**High-intermediate risk (HIR) endometrial cancer:* stage IA (with invasion) and grade 3; stage IB, grade 1 or 2; with either age ≥ 60 or substantial lymph-vascular space invasion (LVSI); stage IB, grade 3 without LVSI; or stage II (microscopic) with grade 1. Est = estimated.

Figure 1B. Decision tree of the molecular-integrated risk profile.



*Patients with multiple characteristics (double classifiers) were designated intermediate risk. MMRd = Mismatch repair-deficiency. For details, see text.

METHODS

Study design and randomization

The PORTEC-4a trial is a multicenter randomized phase 3 trial, led by the Dutch Gynecologic Oncology Group. The trial aims to evaluate vaginal recurrence after adjuvant treatment or observation based on the molecular-integrated risk profile in women with HIR EC, as compared to standard vaginal brachytherapy (VBT), and evaluate quality of life and toxicity in both groups. Eligible women who consent to participation in the PORTEC-4a trial are randomly allocated (1:2) to VBT or the experimental arm using a biased coin minimization procedure with stratification for participating center, tumor grade and type of surgery. The PORTEC-4a trial opened to patient recruitment in June 2016. A total of 500 evaluable patients will be enrolled in the trial. The 54 participants of the previous PORTEC-4 trial design will be included in the analysis by adding those randomized to VBT to the control group (n=36), and those randomized to observation to the experimental arm if their risk profile is favorable. Only approximately 8 women in the observation arm (45% of the 18 in this arm) will have either an intermediate or unfavorable risk profile and will be excluded from the analysis. The first 50 patients who were randomized in the PORTEC-4a trial were included in the pilot phase of the study to evaluate patient acceptability and feasibility of logistics, where after recruitment continued for the main trial endpoints. The trial protocol was approved by the LUMC Ethics Committee (CME P16.054), the Dutch Cancer Society review board (CKTO 2011-5336; amended version) and by the institutional review boards of the participating centers. The trial is registered with the Netherlands Trials Registry (NTR5841), the ISRCTN Registry (ISRCTN11659025) and clinicaltrials.gov (NCT03469674).

Patient selection and eligibility criteria

Women are eligible for the trial when diagnosed with high-intermediate risk (HIR) endometrial cancer, defined as: endometrial cancer of either (1) FIGO stage IA (with invasion) and grade 3; (2) FIGO stage IB grade 1 or 2 with age $\geq$ 60 and/or LVSI; (3) FIGO stage IB grade 3 without LVSI; or (4) FIGO stage II (microscopic) and grade 1. Eligible patients have had surgery using laparoscopic or abdominal hysterectomy and bilateral salpingo-oophorectomy (with or without pelvic lymphadenectomy) and a WHO-performance status of 0-2. Exclusion criteria are non-endometrioid type endometrial cancer, uterine sarcoma, a history of malignancy within 5 years, previous pelvic radiotherapy and an interval of more than 8 weeks between surgery and start of radiotherapy.

Pathology review and molecular-integrated risk profiles

After informed consent and randomization, all histopathological slides and a representative formalin-fixed paraffin-embedded (FFPE) block of the tumor are sent to the Department of

Pathology at LUMC for pathology review and determination of the molecular-integrated profile. Standard items to be determined are histological type and grade, depth of invasion and presence and semi-quantification of LVSI. Immunohistochemistry and molecular analysis are performed to determine the *POLE* (exon 9, 13 and 14) and *CTNNB1* (exon 3) status, L1CAM, p53 and MMR protein expression (MLH1, PMS2, MSH2, MSH6), and, additionally, ER/PR status. During the pilot phase a transition was made in the method of molecular analysis from targeted Sanger sequencing to targeted NGS. In the transition phase, assessment of *POLE* exon 9, 13 and 14 was performed by Sanger sequencing. Later, these exons were included in the Ampliseq Cancer Hotspot NGS panel. In case of loss of MMR-protein expression without *MLH1* promoter hypermethylation (expected in 3-5% of cases[19]), this is reported to the treating physician for patient information and referral to a clinical geneticist for counseling and germline mutation analysis for possible Lynch-syndrome.

The pathology review has to be completed within 2 weeks from randomization, as patients have to start radiotherapy within 8 weeks from surgery. The results of pathology review and the molecular-integrated risk profile are immediately sent back to the local radiation oncologist to determine adjuvant treatment. For patients in the standard arm, a limited set of data (including MMRd and ER/PR) is reported back to the treating center, while the molecular-integrated profile (including all other variables) is reported to the trial database. For all patients who have given informed consent for tissue storage for further translational research, one FFPE-block is stored in the dedicated PORTEC4a tissue repository; all original slides are returned to the local pathology lab. During the pilot phase, pathology review and determination of the integrated profile was conducted at LUMC to ensure uniform procedures and determine the logistical feasibility. After completion of the pilot phase, other regional pathology labs can be authorized to perform the review and determine the profile for trial participants in their region.

Treatment and follow-up

Treatment in the experimental arm is based on the molecular-integrated risk profile: women with a favorable profile are observed after surgery; those with an intermediate profile receive VBT; and those with an unfavorable risk profile receive EBRT (Figure 1). Based on the previous analysis[13], about 55% of those with HIR EC are expected to have a favorable profile, about 40% an intermediate profile and about 5% an unfavorable profile.

Women in the standard arm and those with an intermediate profile in the experimental arm will receive VBT to the vaginal vault (target volume including the upper 3.5-4 cm of the proximal vagina) with a vaginal cylinder and a high-dose-rate (HDR) afterloader. The VBT dose is 21 Gy HDR in 3 fractions of 7 Gy, specified at 5 mm from the applicator surface and top, 5-7 days apart,

with an overall treatment time of 2 weeks. Centers have to complete a dummy-run procedure for vaginal brachytherapy before participation in the trial, and quality assurance is done by evaluation of one treatment plan per year for each participating center.[20] Women in the experimental arm with an unfavorable profile will receive pelvic EBRT to a total dose of 45-48.6 Gy in 1.8-2 Gy daily fractions, 5 times a week, using CT-based intensity modulated radiotherapy planning (IMRT) or a volumetric arc technique (VMAT or RapidArc).

Patients in both arms are evaluated at alternating follow-up visits by their gynecologic oncologist and radiation oncologist every 3 months for the first 2 years, and every 4-6 months up to the 5th year. Information at 7 years is obtained from the GP. In case of recurrence, full evaluation is required and treatment with curative intention is initiated, if appropriate. All patients with recurrent disease remain in follow-up; in case of death, information on its cause is required.

Toxicity is evaluated by the radiation oncologist using CTCAE v 4.0[19] at baseline; at 3-4 weeks after completion of brachytherapy or EBRT; and at each follow-up visit. Assessment of health-related quality of life (HRQL) is done by use of the EORTC QLQ C-30 core questionnaire and endometrial cancer-specific EN24 module in both arms at baseline, at 6 weeks, and at 6, 12, 18, 24, 36, 60 and 72 months from randomization.

Trial endpoints and statistical design

The primary outcome of the PORTEC-4a trial is the 5-year cumulative incidence of vaginal recurrence. Secondary outcomes are pelvic and distant recurrence rates, 5-year vaginal control rate including treatment for relapse, 5-year recurrence-free and overall survival, adverse events, patient-reported symptoms and quality of life, and endometrial cancer-related healthcare costs.

To estimate vaginal recurrence in both groups with sufficient precision and to exclude a clinically relevant difference, the trial is based on a non-inferiority design with an equivalence margin of 7%. For a total of 500 evaluable patients, with 334 in the experimental arm and 167 patients in the standard arm, the estimated power (based on 10.000 simulations) is 84.4% (α=0.05). An additional power calculation was done comparing patients with a favorable profile in the standard arm (receiving VBT) versus those with a favorable profile in the experimental arm (receiving observation), using a non-inferiority design with an equivalence margin of 8.5%. The power for this comparison is dependent on the actual 5-yr cumulative incidence of VR in the favorable subgroup of the experimental arm (power >75% for VR <5%) and analysis will be largely descriptive, estimating the difference with standard error <2.5. The competing risk method will be used with death, pelvic and distant recurrences as competing events for vaginal recurrence. The analysis will be performed according to intention-to-treat. Analysis of HRQL will be based on treatment received, including participants with a valid

baseline and at least one follow-up questionnaire. EC-related healthcare costs, including the costs of the initial treatment by randomized arm, follow-up, care associated with adverse events and with treatment of recurrence, will be evaluated and compared.

Evaluation of the pilot phase

After the first 50 included patients, the results of the pilot phase were evaluated. Endpoints for the pilot phase are patient acceptability of the trial and feasibility of obtaining the molecular-integrated profile within two weeks after randomization. Pathology logistics were evaluated by assessment of all logistical data of the 32 patients that were randomized to the experimental arm. Additional logistical problems concerning the pathology review were evaluated by interviewing the review-pathologists. To evaluate patient acceptability, the screening logs kept by the participating centers on patient assessment and reasons for trial acceptance or refusal were evaluated.

RESULTS

Participants

The first 50 patients of the PORTEC-4a trial were included between June 10th 2016 and June 12th 2017, in 10 radiation oncology centers in The Netherlands. Of those, 32 patients were randomly assigned to the experimental arm and 18 to the standard arm. Currently, 16 centers in The Netherlands have been opened for inclusion, of which some quite recently, and 12 have been actively including patients. A total of 138 patients have been accrued to date (July 2018), of whom 91 were randomly allocated to the experimental arm and 47 to the standard arm (Figure 2).

Patient acceptance

Evaluation of the screenings logs of all participating centers showed that 145 eligible women had been informed about the trial in 13 participating centers. 50 of those 145 (35%) women provided informed consent. Patient accrual ranged from 0 to 57% per center. The remaining 95 of the 145 eligible patients were informed about the trial but did not participate for the following reasons: 41 (43.2%) did not want to participate in any trial and 31 (32.6%) did not want to risk receiving no adjuvant treatment. In 9 (9.5%) cases the radiation oncologist forgot to inform the patient about the trial, and 8 (8.4%) patients had difficulty understanding the trial. Four (4.2%) patients refused participation because of the possibility of receiving external beam radiotherapy instead of vaginal brachytherapy, and 2 (2.1%) patients did not want to participate in quality of life questionnaires (Table 1). Physicians reported that consenting patients were motivated by the added information on their individual risk and necessity to undergo adjuvant treatment, and by contributing to scientific knowledge informing future treatments.

Figure 2. Cumulative accrual of the PORTEC-4a trial.

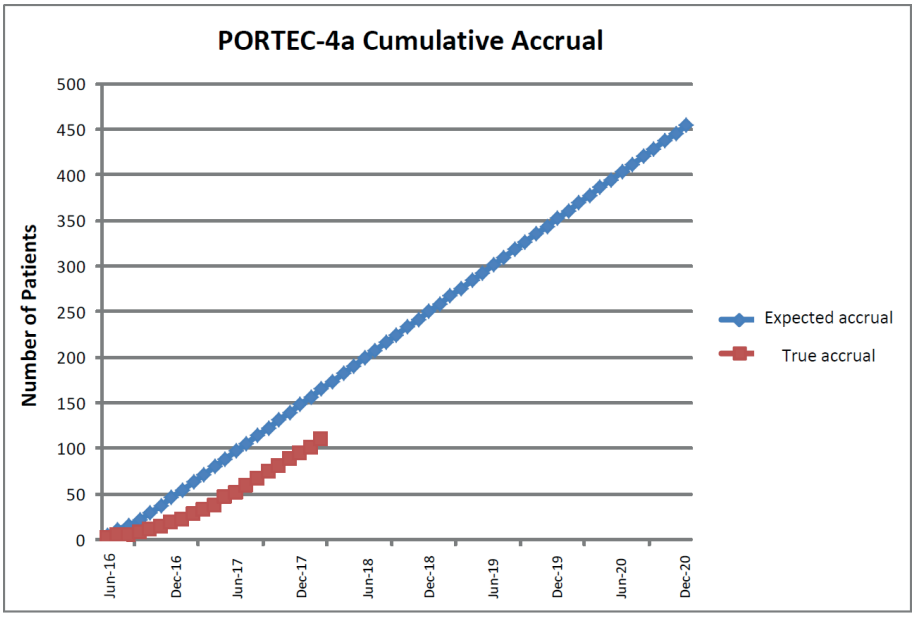


Table 1. Reasons for not participating.

Reasons	Number
Refusal to participate in any trial	41 (43.2%)
Not willing to risk observation	31 (32.6%)
Physician forgot to ask	9 (9.5%)
Difficulty understanding	8 (8.4%)
Not willing to risk EBRT*	4 (4.2%)
Not willing to fill in questionnaires	2 (2.1%)
Total	**95**

** EBRT: external beam radiotherapy*

Logistics of pathology review

By protocol, pathology review had to be performed within 14 days from randomization. Analysis of logistical data of the 32 patients that were randomized to the experimental arm showed an average time between randomization and receipt of all requested materials at the department of Pathology in the LUMC of 5.8 days (range: 1-16 days). Of these 32 cases, 21 were included by institutions other than LUMC. In 7 out of 21 cases (21.9%), material had to be requested more than once. Overall, the average time between randomization and determination of the molecular-integrated profile was 10.2 days (range: 1-23 days); without cases from the LUMC, the average time was 12.2 days (range: 5 – 23 days). In 5 of the 32 patients (15.6%), pathology review took

more than 2 weeks. Causes for the determination of the molecular-integrated profile exceeding the protocol requirement of 2 weeks were: delayed receipt of the requested materials (>7 days after randomization) in 4 cases, and extended duration of the Next-Generation Sequencing (NGS) panel in 1 case (Table 2).

By interviewing the review pathologists on the logistics of the molecular-integrated profile, the main issues were found to be that (1) the logistics of ensuring prompt receipt of all required materials without patient identifiers (in view of the trial setting) involved repeated explanation and multiple phone calls were sometimes needed in the early phase of the trial; and (2) during the pilot phase *POLE* (exon 9, 13 and 14) were added to the next generation sequencing (NGS) panel, which resulted in a slightly longer turnaround time of results as compared to the targeted Sanger sequencing of *POLE* as was performed during the development of the test.

Table 2. Cases with delayed (>14 days) result of the profile.

Number of days	Main reason
2	15 days for NGS*
3	7 days until receipt, 10 days for NGS
4	3x request for material, 12 days until receipt#
6	16 days until receipt#
9	2x request for material, 15 days until receipt

** NGS: Next-Generation Sequencing; in the early phase, NGS runs were only done once a week.*
 # At this time, the Sanger Sequencing method was used to determine the profile

DISCUSSION

In the pilot phase of the PORTEC-4a trial the feasibility and patient acceptance of the trial design were evaluated, as the trial randomizes women with HIR EC between standard VBT and treatment based on an individual molecular-integrated risk profile. Evaluation of the acceptance of the trial design by eligible women showed a patient inclusion rate of 35%. Most common reasons not to participate in the trial were that patients were either not willing to participate in any randomized trial, or preferred to receive standard care.

Evaluation of trial logistics showed that the large majority (84%) of the molecular-integrated risk profiles were assessed within the required timeframe of 14 days. Causes for delay in the logistics were delayed receipt of the requested materials and the turnaround time of NGS. Overall, the PORTEC-4a trial proved to be feasible and patient inclusion was continued at a slightly increased rate due to more centers being activated.

Patient acceptance of the trial design was satisfactory with a patient inclusion rate of 1 in 3 eligible women, which was in accordance with the study protocol expectations. This was substantially higher than in the previous PORTEC-4 design, wherein centers reported that only 1 in about 10 to 15 eligible women accepted randomization, due to their preference of adjuvant VBT over observation, even for a minimal benefit. This is in line with the patient preference study, done in the scope of the PORTEC-4 trial, in which women chose VBT over observation at a lower minimal benefit than clinicians (median 0 vs. 8%).[11] A study on decision making in breast cancer patients showed that women felt more in control of their disease, when opting for an active treatment compared to observation.[20] Chapple et al. investigated treatment decision making in men with prostate cancer and described that patients were afraid to be observed instead of treated and felt pressure from their relatives to choose an active treatment over observation.[21]

The new trial design implemented the recent knowledge of the molecular heterogeneity of EC, including the four molecular-genetic subclasses described by the TCGA and other negative prognostic risk factors such as LVSI, L1CAM and mutations in exon 3 of *CTNNB1*.[12, 14-18] Eligible women accepted the new trial design that evaluated use of the molecular-integrated profile to determine adjuvant treatment much more often; the inclusion rate of 35% included not only patient acceptance but also initial logistical issues.

Currently, 138 patients have been recruited to the trial in the first 2 years. In the Netherlands, 16 centers are open for inclusion, and several international groups have shown interest in participating in the trial.

Evaluation of trial logistics showed that delayed receipt of requested slides and FFPE blocks was the most common difficulty initially. Due to the trial setting, the materials had to be requested without patient identifiers (only the local pathology number), and repeated phone calls and/or emails were sometimes needed. Introduction of standard email text clarifying the urgent request of materials helped to improve this, as well as increased awareness of the trial at other pathology laboratories in the initial phase. Another logistical challenge was the transition from targeted Sanger sequencing to targeted NGS. While Sanger sequencing is a relatively cheap method yielding fast results (<24 hours), NGS is associated with higher costs and has a longer turnaround time, which also depends on the number of NGS-runs initiated per week in the laboratory. We transitioned to targeted NGS for PORTEC-4a as we anticipated that other laboratories will have easy access to NGS platforms, whereas the use of Sanger sequencing in diagnostic pathology is rapidly decreasing. Currently the NGS panel includes *POLE* (exon 9, 13 and 14) and has been fully integrated in the workflow, with 2-3 runs per week, ensuring timely results.

According to the current Dutch guidelines, all women with HIR endometrial cancer should be treated with adjuvant VBT.[2] LVSI has been shown to be an essential risk factor and has been

introduced in the most recent version of the ESMO-ESGO-ESTRO consensus recommendations.[22] However, the recent knowledge on the molecular genetic basis of endometrial cancer has become available by the Cancer Genome Atlas studies, with establishment of four distinct molecular subgroups associated with prognosis, has not yet been introduced into the clinic. Several groups have shown that the four molecular subgroups can be determined in clinical practice using surrogate markers on FFPE tissues and confirmed their prognostic significance.[13, 16] However, these molecular risk factors have not yet been evaluated in clinical practice to determine patient management. Moreover, both our group and the Vancouver group have shown that the molecular risk factors should be integrated with other major risk factors to obtain the strongest prognostic significance and highest clinical relevance.[13, 23]

The PORTEC-4a trial is the first prospective randomized trial that investigates the use of an integrated molecular risk profile in endometrial cancer to determine adjuvant treatment in the clinic. PORTEC-4a aims to avoid overtreatment by omitting VBT in women with endometrial cancer with traditional clinicopathological high-intermediate risk factors, but favorable risk by the molecular-integrated profile. On the other hand, the trial is also aiming to avoid undertreatment of the few women with high-risk factors such as substantial LVSI, *TP53* mutation or L1CAM overexpression by using EBRT in these cases.[14, 15] If the PORTEC-4a trial shows similar local control rates for both the molecular-integrated risk profile arm and the standard VBT arm, integrated risk assessment will become standard practice, tailoring treatment on a more individual basis and sparing health care costs. Furthermore, these women will be spared the burden and toxicity of vaginal brachytherapy, as approximately half of all women with HIR EC currently undergoing VBT will be observed after surgery (Figure 1).

Other opportunities that will emerge with assessment of molecular-integrated risk profiles lie within the fields of pre-operative staging and tailored treatment of metastatic disease. Studies that assessed the concordance of pre-operative curettage samples and surgical specimens showed that molecular alterations detected in curettage samples reliably predicted the alterations found in the subsequent hysterectomy specimens.[24, 25] Pre-operative assessment of molecular risk factors may aid patient counseling and enable tailoring of treatment, especially in the case of high-risk features, for example by more extensive diagnostic work-up (PET-CT scanning), tailored lymph node assessment or even neo-adjuvant treatment.[26] As the molecular groups with *POLE* mutation and mismatch repair deficiency have been shown to be highly immunogenic, first small studies of targeted treatment by checkpoint inhibition have been done, showing promising results.[27, 28] However, especially for molecular high-risk features and non-endometrioid histologies, clinical data are still limited and studies addressing the role of the molecular integrated classifiers to inform and direct treatment of specific high-risk subgroups,

both in treatment of primary and recurrent disease, are needed.

In conclusion, the PORTEC-4a trial design has been proven feasible by assessment of the pilot phase and recruitment is ongoing. PORTEC-4a is the first trial to assess the use of an integrated molecular profile to determine adjuvant treatment, and other studies using molecular-based treatment are eagerly awaited.

ACKNOWLEDGEMENTS

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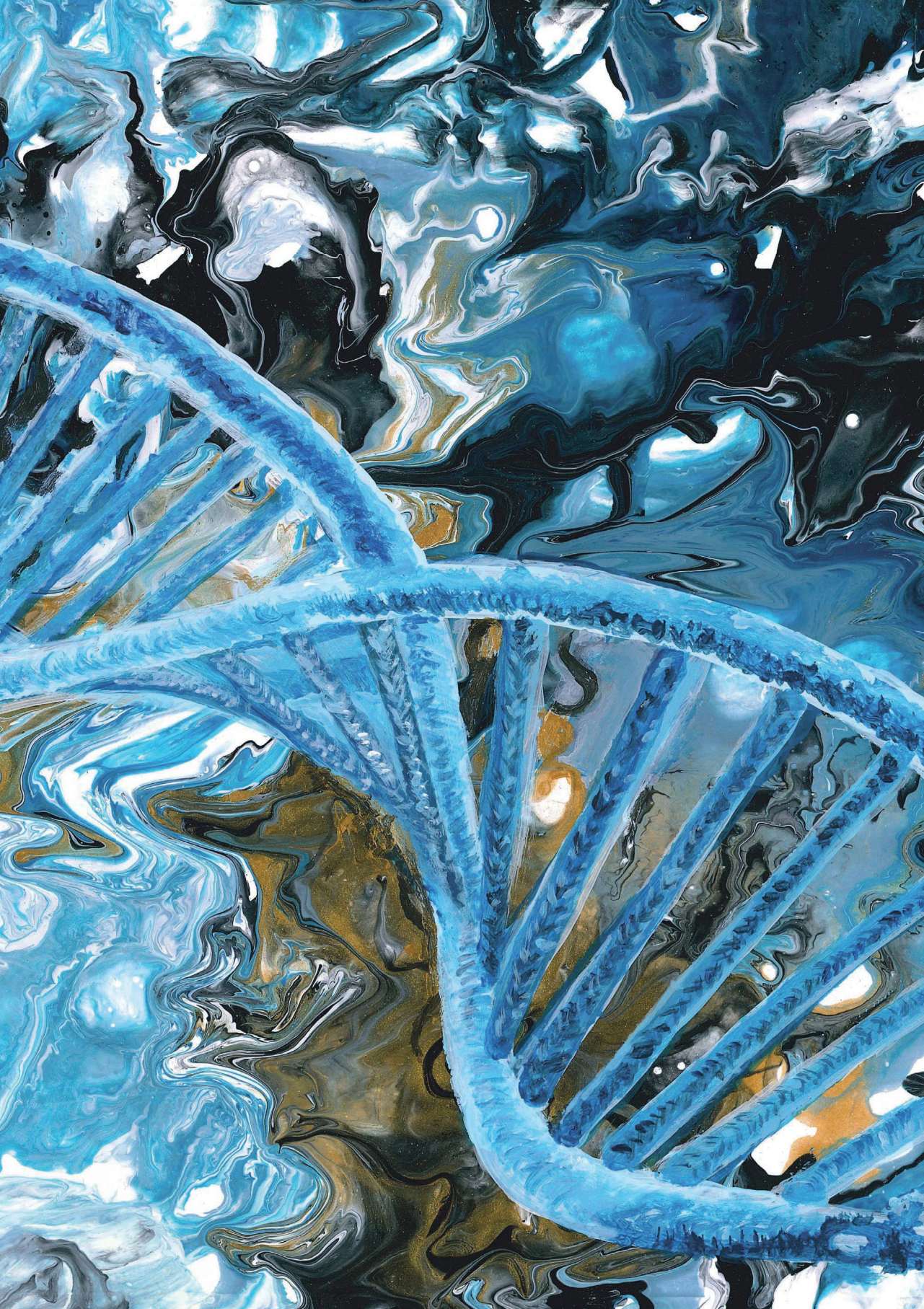
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CHAPTER 4

BRACHYTHERAPY QUALITY ASSURANCE IN THE PORTEC-4A TRIAL FOR MOLECULAR-INTEGRATED RISK PROFILE GUIDED ADJUVANT TREATMENT OF ENDOMETRIAL CANCER

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ABSTRACT

Objective: The PORTEC-4a trial investigates molecular-integrated risk profile guided adjuvant treatment for endometrial cancer. The quality assurance programme included a dummy run for vaginal brachytherapy prior to site activation, and annual quality assurance to verify protocol adherence. Aims of this study were to evaluate vaginal brachytherapy quality and protocol adherence.

Methods: For the dummy run, institutes were invited to create a brachytherapy plan on a provided CT-scan with the applicator in situ. For annual quality assurance, institutes provided data of one randomly selected brachytherapy case. A brachytherapy panel reviewed and scored the brachytherapy plans according to a checklist.

Results: At the dummy run, 15 out of 21 (71.4%) institutes needed adjustments of delineation or planning. After adjustments, the mean dose at the vaginal apex (protocol: 100%; 7 Gy) decreased from 100.7% to 99.9% and range and standard deviation (SD) narrowed from 83.6-135.1 to 96.4-101.4 and 8.8 to 1.1, respectively. At annual quality assurance, 22 out of 27 (81.5%) cases had no or minor and 5 out of 27 (18.5%) major deviations. Most deviations were related to delineation, mean dose at the vaginal apex (98.0%, 74.7-114.2, SD 7.6) or reference volume length.

Conclusions: Most feedback during the brachytherapy quality assurance procedure of the PORTEC-4a trial was related to delineation, dose at the vaginal apex and the reference volume length. Annual quality assurance is essential to promote protocol compliance, ensuring high quality vaginal brachytherapy in all participating institutes.

INTRODUCTION

The primary treatment for women with endometrial cancer (EC) is abdominal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy, followed by adjuvant radiotherapy depending on clinicopathological risk factors. Currently, four risk groups of EC have been defined: low, intermediate, high-intermediate (HIR) and high-risk.[1]

For women with HIR EC the standard adjuvant treatment is vaginal brachytherapy (VBT), which is based on previous randomised trials. VBT was shown to be equally effective compared to external beam radiotherapy (EBRT) in local control and survival, with a markedly lower toxicity profile.[2-6] However, there is still considerable overtreatment, as approximately 7-10 women with HIR EC need to be treated with adjuvant VBT to prevent one recurrence.[7] Better selection of patients at risk of recurrence may play an important role in reducing overtreatment.

The Cancer Genome Atlas Group (TCGA) has discovered four specific molecular subgroups of EC, with each subgroup having a distinct prognosis.[8] Using surrogate markers, these molecular subgroups have been validated in independent EC cohorts and have been shown promising in guiding decisions on adjuvant treatment.[9-12] The role of molecular factors in decision making on adjuvant treatment of HIR EC is currently being investigated in the ongoing international randomised PORTEC-4a trial.[13] In this trial, women with HIR EC are stratified in a favourable, intermediate or unfavourable profile based on molecular and clinicopathologic risk factors and consequently treated with no adjuvant treatment, VBT or EBRT, respectively.[14]

In view of the use of VBT in the standard arm and for the women with intermediate profile in the experimental arm, approximately 60% of the PORTEC-4a trial population will receive VBT, a single channel brachytherapy plan using a vaginal cylinder. The VBT planning is based on delineation of the target volume and organs at risk on CT- or MRI-images during at least one fraction. Imaging with CT or MRI with a vaginal cylinder in situ can provide valuable data on dose distribution to the target volume and rectum and bladder that can be used for evaluation of VBT related toxicity. Since institutes had limited experience with delineating on CT- or MRI-scans for single channel VBT, and to ensure uniform high-quality brachytherapy in the PORTEC-4a trial, a dedicated VBT quality assurance (QA) programme, including a dummy run procedure, was implemented in the trial. Especially for radiotherapy trials in general, QA is considered essential as a decrease in therapeutic effectiveness and impaired trial outcomes by protocol deviations have been reported.[15,16] Furthermore, QA increases trial protocol adherence and treatment uniformity, and therewith ensures optimal treatment in both arms which leads to more reliable trial outcomes.[17-23]. The aim of the current study was to investigate protocol adherence by evaluating results of the dummy run procedure and three annual QA rounds in the international PORTEC-4a trial.

METHODS

Trial objective

The main objective of the randomised PORTEC-4a trial is to evaluate adjuvant treatment directed by molecular-integrated risk profiles for women with HIR EC, defined as: either (1) FIGO stage IA (with invasion) and grade 3; (2) FIGO stage IB grade 1 or 2 with age ≥60 and/or LVSI; (3) FIGO stage IB grade 3 without LVSI; or (4) FIGO stage II (microscopic) and grade 1.

Based on three risk profiles, women in the experimental arm will receive either no further treatment when favourable, adjuvant VBT when intermediate, or EBRT when unfavourable. Women randomised to the standard arm receive adjuvant VBT. Details on patient selection, treatment and trial logistics have been published previously.[13,14]

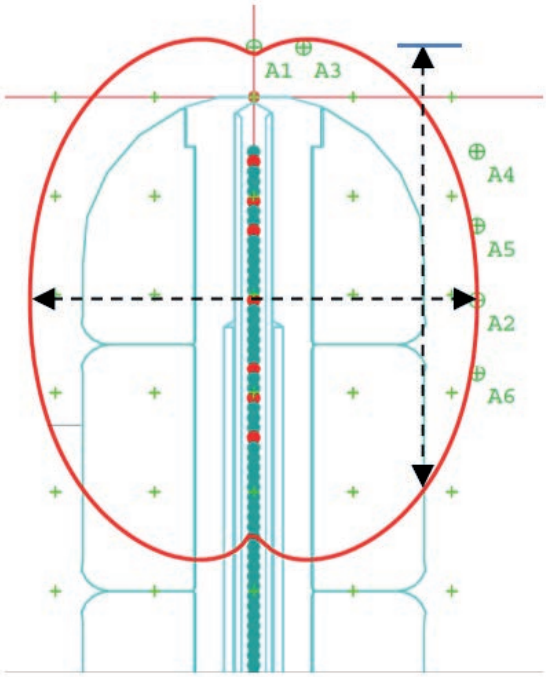
Vaginal brachytherapy in the PORTEC-4a trial

Vaginal brachytherapy should start within 6-8 weeks from the date of surgery. High dose rate (HDR) brachytherapy is given with a vaginal cylinder with one active central channel. Prior to cylinder insertion vaginal examination should take place to verify if the surgical scar has healed sufficiently. Preferably the cylinder with the largest diameter that fits comfortably is used to ensure optimal contact with the vaginal mucosa, resulting in an optimal dose gradient at the surface. After the cylinder placement, correction to a horizontal position is recommended to avoid unnecessary dose to the rectum or bladder.[24]

At the first brachytherapy session a CT- or MRI-scan with the applicator in situ is made for delineation of the CTV and organs-at-risk (OARs) and treatment planning. The CTV consists of the vaginal wall and apex of the upper 1/3 of the vagina; for the majority of patients this corresponds to a length of approximately 3.5 cm. The CTV is delineated as a ring structure that surrounds the applicator with a 3 mm margin. OAR include the bladder, rectum, sigmoid and small bowel (loops).

For treatment planning, a library of standard plans per applicator type, diameter and target length are used, with 6 dose reference points, A1 to A6 (Figure 1). Points A1 and A3 are located at the top of the cylinder at 5 mm from the cylinder surface, with A1 at the central axis and A3 5 mm laterally from A1. Parallel to the central axis at 5 mm from the cylinder surface points A2 and A4 to A6 are placed. A2 is located halfway along the length of the active dwell positions, A4 at the first possible dwell position and point A5 and A6 in between A4 and A2 and caudal of A2, respectively (Figure 1).

Figure 1. Dose distribution for a vaginal cylinder diameter 3.5cm.



100% isodose line (red). Dose is specified to point A2; average dose of A1+A3 should be approximately 100%; dose to A1 >90% and A3<110%; A4-6 aim for dose reporting with the aiming to reach >95%. Reference length/width (dotted arrows), reference length should aim for 40-45mm, with a maximum of 50mm.

Three fractions of 7 gray (Gy), prescribed to dose point A2, should be delivered within an overall treatment time of 2 weeks. To ensure an adequate dose in the apical vaginal mucosa and compensate for the anisotropy in the longitudinal direction of the 192-Iridium source, the dose in point A1 should be at least 90% and in A3 110% at maximum, with an average dose in A1 and A3 of 100% (7 Gy). A symmetrical loading pattern of the cylinder in the cranial-caudal direction is recommended to facilitate treatment planning, but not mandatory. The reference volume length (RVL) represents the length of the vaginal wall that receives 100% or more and is measured from the top of the 100% isodose line to the point where it enters the cylinder caudally. The RVL should be around 40-45 mm, with a maximum of 50 mm, ensuring sparing of the lower vaginal wall. The mean doses to 90% and 98% of the CTV (D90 and D98) and the maximum dose to 2cc (D2cc) of the OARs, should be recorded.

Brachytherapy QA-procedure

Dummy run procedure

Before site activation, all participating institutes must have filled in a pre-trial credentialing questionnaire and have performed a dummy run procedure. The questionnaire addresses items such as imaging modality, type of afterloader, cylinder and treatment planning software (TPS) and VBT staff. For the dummy run DICOM-images of a pelvic CT and MR scan with a cylinder in situ are sent to each institute. The local brachytherapy teams are requested to delineate the CTV and OAR conforming to the trial protocol, and to create a brachytherapy plan by using their own TPS. This plan is evaluated by a central QA-panel consisting of two radiation oncologists and one medical physicist specialised in brachytherapy (R.A.N.; C.L.C.; E.A.), a radiation oncologist in training (B.G.W.) and an advanced practitioner brachytherapy (M.S.L.). In case of protocol deviations feedback is sent and the dummy run procedure is repeated when necessary. Upon successful completion of the dummy run procedure, institutes can be activated for the trial.

Annual quality assurance

Annual QA consists of evaluation of a VBT plan of one randomly selected PORTEC-4a case number that has received VBT in the trial in the specific centre. The local team is asked to provide the anonymised CT- or MRI-scan that was used for VBT planning, the DICOM RT-structures, planning and dose distribution, including dose to the A-points, OARs and CTV. Alongside the DICOM-data, updated credentialing questionnaires are requested to objectify changes in VBT components or staff. All requested data, images and plans were evaluated by the QA-panel.

Analysis

According to a QA-checklist all plans of both the dummy run and annual QA were scored on delineation, treatment planning and dose distribution. Annual QA was additionally scored on applicator positioning. Results for each of the items were categorised as fully compliant, partly compliant, in case of a minor protocol deviation, or not compliant, in case of a major deviation. When one or multiple items were scored as partly or not compliant at the dummy run, a revised VBT plan was requested and evaluated. In case of major deviations at annual QA, a teleconference was held for additional explanation and discussion of the feedback, and the next new case number of that particular institute was requested for an extra QA.

On all received data of both the dummy run and the three annual QA procedures descriptive analyses were performed for evaluation of protocol compliance, by comparing the first and final dummy run plan and the annual QA, for the following dose parameters: mean percentage dose, with 100% being 7 Gy, the dose range and standard deviations of all A-points, D98 and D90 of the CTV and the D2cc of the OARs.

To estimate the influence of inter-observer delineation variation on the dose parameters, all delineated structures of the accepted plan of dummy run were projected on the dummy run CT-scan with the LUMC applicator reconstruction and LUMC dose plan. This resulted in the same dose distributions for each case, but variating delineations of the CTV and OARs. For this sub-analysis the mean dose, dose range and standard deviation were recorded. The two institutes with MRI were not included in this analysis.

RESULTS

Participants

Between June 1st, 2016 and March 30th, 2020, 327 patients have been included in the PORTEC-4a trial in 19 institutes in 5 countries. Currently, 21 institutes have successfully completed the dummy run. For the dummy run, 19 institutes used CT for brachytherapy planning and two MRI. Three different types of treatment planning systems and three different HDR afterloaders are used (Table 1). Institutes reported the use of several types of single channel vaginal applicators, varying from standard applicators produced by Elekta or Varian, to dedicated applicators, produced in their own institution.

Table 1. Brachytherapy characteristics at dummy run.

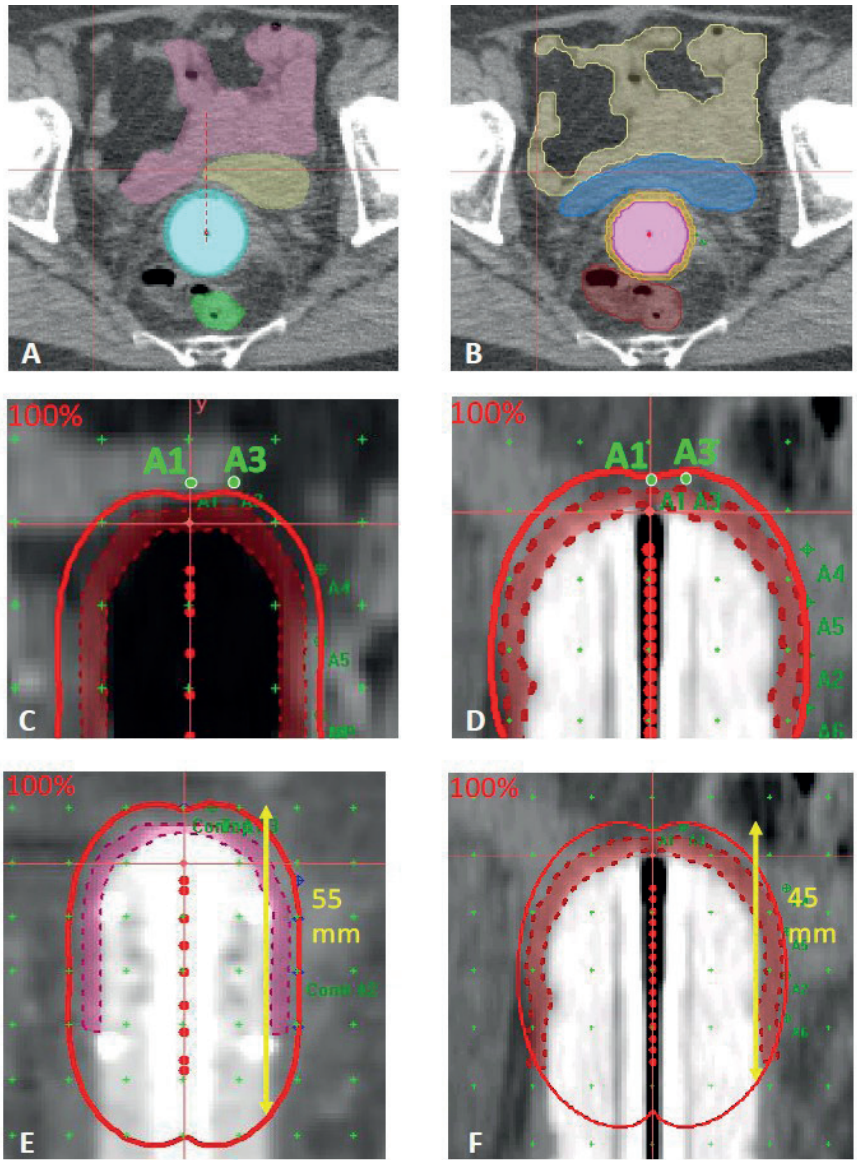
	Number of institutes
Dummy run accepted	
First plan	6
Final plan	15
Imaging modality	
CT	19
MR	2
Brachytherapy planning system	
Oncentra	14
Flexiplan	3
Brachyvision	4
Type of afterloader	
Flexitron	10
Microselectron	6
Gammamed	5

Dummy Run procedure

In total, 21 institutes successfully completed the dummy run procedure and participate in the PORTEC-4a trial. Six out of 21 (28.6%) VBT plans were accepted after the first run, 15 (71.4%) needed to resubmit for minor or major adjustments. Common aspects for revisions were: CTV or OAR delineation (Figure 2A and B), dose planning (Figure 2C-E) and applicator reconstruction. After adjusting delineation of the CTV and/or dose planning of the VBT plans, the mean dose in the dose prescription point (A2) decreased from 101.5% to 100.5% of the prescribed dose, with 7 Gy being 100%, and the range and standard deviation (SD) of the mean narrowed from 100.0-109.7% to 99.5-105.4% and 2.9 to

1.3, respectively. For the dose at the vaginal apex (mean dose in A1 + A3) the mean decreased from 100.7% to 99.9%, the range from 83.6-135.1% to 96.4-101.4%, and the SD from 8.8 to 1.1 (Table 2). In table 3 the effect of inter-observer delineation variation on the dose parameters is displayed.

Figure 2. Most common reasons for feedback.



Delineation: organs at risk and CTV (A). CTV should be a ring structure surrounding the applicator and all bowel loops should be included (B). Treatment planning: Mean dose in point A1+A3 (C) should be 100% (D) and reference volume length (E) should be around 40-45mm (F).

Table 2. Dose parameters at dummy run procedure and annual QA.

Dose parameters	Dummy run first plan* (N=21)	Dummy run final plan (N=21)	Annual QA (N=27)
A2 (Aim 100%)			
Mean dose** (SD)	101.5 (2.9)	100.5 (1.3)	100.4 (1.7)
Range	100.0-109.7	99.5-105.4	99.0-108.7
A1 (Aim 90-95%)			
Mean dose (SD)	93.1 (8.8)	92.0 (1.7)	90.2 (7.0)
Range	75.8-126.8	89.3-94.8	67.8-102.9
A3 (Aim 105-110%)			
Mean dose (SD)	108.2 (9.0)	107.8 (1.8)	105.7 (8.4)
Range	91.3-143.4	102.5-110.0	81.7-125.5
Mean A1+A3 (Aim 100%)			
Mean dose (SD)	100.7 (8.8)	99.9 (1.1)	98.0 (7.6)
Range	83.6-135.1	96.4-101.4	74.7-114.2
A4			
Mean dose (SD)	83.2 (7.1)	84.9 (6.9)	87.1 (6.2)
Range	73.8-106.0	76.6-99.0	76.7-99.1
A5 (Aim 95-100%)			
Mean dose (SD)	96.4 (3.2)	96.8 (3.7)	98.5 (2.9)
Range	91.0-103.8	93.0-110.2	94.0-105.1
A6 (Aim 95-100%)			
Mean dose (SD)	97.3 (3.2)	96.9 (3.1)	98.7 (3.5)
Range	88.9-102.1	88.9-102.1	87.6-104.6
D90* **			
Mean (SD)	7.9 (0.8)	8.0 (0.9)	8.0 (0.9)
Range	6.3-9.4	6.3-9.4	5.6-9.7
D98			
Mean (SD)	7.2 (0.9)	7.3 (0.9)	7.3 (1.2)
Range	5.1-8.6	5.8-8.6	4.0-9.2
Bladder D2cc			
Mean (SD)	5.2 (0.5)	5.3 (0.5)	5.9 (0.8)
Range	4.3-6.0	4.3-6.0	4.8-7.7
Rectum D2cc			
Mean (SD)	6.1 (0.5)	6.1 (0.5)	6.0 (0.6)
Range	4.7-7.1	5.0-6.9	4.0-7.2
Sigmoid D2cc			
Mean (SD)	3.7 (1.2)	3.6 (1.2)	2.9 (1.2)
Range	2.1-6.9	1.4-6.4	0.5-5.1
Small bowel D2cc			
Mean (SD)	5.5 (1.6)	5.3 (1.8)	2.8 (1.8)
Range	1.1-7.8	0.9-7.3	0.8-6.9

**Institutes for which the first dummy run plan was accepted have been listed in both columns (N=6)*

***Mean percentage dose, with 100% being 7 Gy. ***Dose in Gy.*

Table 3. Variation in dose parameters resulting from inter-observer differences in delineation at the dummy run.

Dose parameter	Mean* (SD)	Range
CTV D90	8.1 (0.5)	7.4-9.2
CTV D98	7.3 (0.6)	6.3-8.4
Rectum D2cc	5.9 (0.5)	4.7-6.8
Bladder D2cc	5.0 (0.6)	4.4-5.6
Sigmoid D2cc	3.5 (0.9)	2.1-6.1
Small bowel D2cc	5.6 (0.8)	4.1-6.8

**Dose in Gy.*

Brachytherapy annual QA

Three annual QA rounds have been performed between September 2017 and February 2020, for which 7, 13 and 7 VBT plans were evaluated in the first, second and in the first part of the third round, respectively. Of 27 requested VBT plans, 22 (81.5%) were accepted with no or minor feedback, while for five (18.5%) plans a teleconference was held for discussion of the feedback, and a new VBT plan of a subsequent case was requested. Most common items for feedback were: CTV delineation (n=16; CTV length longer than 4.0 cm, or not delineated as a ring structure, or with a margin of more than 3 mm), average dose in points A1 and A3 other than 100% (n=13; 5 partly (100% +/- 3%) and 8 not compliant (100% +/- >3%), see Figure 2C and D), and RVL of more than 50 mm (n=19, see Figure 2E and F). Other feedback items addressed applicator positioning (n=8), suboptimal contact with the vaginal mucosa (n=5; air or contrast surrounding the applicator), and delineation of the OAR (n=10, see table 4).

The treated volumes in the annual QA are displayed in Table 2. The mean dose in the dose prescription point (A2) was 100.4% (range 99.0-108.7%, SD 1.7), and at the vaginal apex (mean A1+A3) 98.0% (range 74.7-114.2%, SD 7.6). The mean RVL was 53.8 mm, ranging from 44.3 to 70.0 mm. Mean D90 and D98, respectively, of the CTV were 7.9-8.0 Gy and 7.2-7.3 Gy, respectively, in both the dummy run and the annual QA rounds. The mean D2cc of the rectum ranged from 6.0 to 6.1 Gy in both dummy run and QA, and the mean D2cc of the bladder, sigmoid and small bowel varied from 5.2 to 5.9 Gy, 2.9 to 3.7 Gy and 2.8 to 5.5 Gy, respectively (Table 2).

Table 4. Evaluation of the annual QA.

Items	Fully compliant	Partly compliant*	Not compliant*
Applicator positioning			
Position and angle of cylinder	19	2	6
Contact of cylinder to vaginal mucosa	22	1	4
Delineation			
CTV delineation	11	11	5
OAR delineation	17	8	2
Treatment planning			
Reconstruction	24	1	2
Position of A points	20	3	4
Prescribed dose in point A2	22	3	2
Symmetry of loading pattern	18	0	9
Evaluation of dose distribution			
Average dose in A1+A3 = 100%	14	5	8
Dose in point A1 $\geq$ 90% and/or A3 $\leq$ 110%	17	6	4
Reference length/width	8	15	4
CTV D90/D98	19	1	7
OAR D2cm3	24	3	0

**scored according to the detailed description in the trial protocol*

QA-rounds compared to Dummy Run

Several changes have been observed in the QA-questionnaires: two institutes changed to a different cylinder applicator, two to another type of afterloader, and three institutes changed their TPS. In five institutes there was a change of brachytherapy staff; two medical physicists and three radiation oncologists were replaced.

DISCUSSION

Analysis of the dummy run procedure for vaginal brachytherapy in the PORTEC-4a trial showed that 71.4% of the initially submitted VBT plans needed adjustments to fulfil trial protocol requirements. With the revised VBT plans, an increase in protocol adherence and a decrease in inter-observer delineation and/or dose planning variability were observed, which resulted in more uniform VBT plans. Evaluation of the annual QA of randomly selected VBT plans per centre showed that 18.5% had major protocol deviations, suggesting that a successful dummy run procedure does not rule out major protocol deviations during the trial.

In this quality assurance study, most common reasons for feedback were delineation of the CTV and OAR, the average dose at the vaginal apex (dose points A1 + A3) and the reference volume length (RVL). Dose points A1 and A3 represent the vaginal vault area which is essential for the target volume. These dose points are aimed to obtain a uniform and reproducible dose

distribution at 5 mm from the apex, even with use of different types of cylinders, sources and treatment planning systems in a randomised multicentre trial. The dose at the apex is essential, not only because approximately over 75% of all recurrences occur at the vaginal apex, but also because a higher dose in point A3 could lead to increased toxicity due to the adjacent bowel loops.[25-27] The RVL directly displays the actual length of the vaginal wall receiving 100% of the dose. The mean RVL in this study was 53.8 mm, while when following the trial protocol, the RVL should range between 40 and 50 mm. In case of an increased RVL, a longer segment of the vagina receives significant dose. This observation led to a general feedback to make all participating institutes aware of this and re-emphasise the importance of the trial planning aims.

Minor feedback items addressed the applicator placement and applicator diameter. When the applicator was placed ventrally or dorsally this could lead to higher doses to the bladder or rectum.[24] In 5 out of 27 reviewed cases the diameter of the vaginal applicator seemed relatively small and air gaps or contrast surrounded the applicator, directly affecting the dose distribution. A previous study showed an average dose reduction to the vaginal mucosa of 27% when air gaps were present and stressed that air gaps of more than 2mm can lead to a decrease in dose to the vaginal mucosa, which in turn may result in an increased risk of local recurrence. Institutes were provided feedback to ensure that an attempt is made to reposition the applicator or to use a larger diameter applicator for more optimal contact to the vaginal mucosa. However, the presence of air gaps has not been related to clinical outcome, as a wide range of dose and fractionation schedules for VBT has been proven effective.[28-31]

Data of dose parameters showed improvements in the dose range between the first and the final plan of the dummy run procedure for the essential dose points A1, A2 and A3, indicating the increased protocol adherence. However, at annual QA, one or more years after the initial dummy run, an increased variability in dose distribution and in dose to points A1, A2, A3 and A6 was observed, also at institutes with a large case load. Possible explanations for this could be institutional changes in type of applicator, afterloader, TPS or VBT staff, that were recorded in the questionnaires; adherence to a local VBT protocol; unfamiliarity with CTV delineation for single channel VBT or unfamiliarity with the trial protocol due to infrequent inclusion. This indicates that continuous QA is essential to ensure protocol adherence in the years after the initial dummy run.

The range and standard deviation of dose parameters D90 and D98 of the CTV and D2cc of the OAR remained similar in the first and final plan of the dummy run, even after adjustments of the delineation and/or VBT planning. This could be explained by the impact of delineation variations on these parameters. Additional analysis showed that when eliminating treatment planning variation, by projecting delineations of all institutes on one standard VBT plan, similar

standard deviations and ranges were found for CTV D90/98 and D2cc of the OAR in the accepted plans. This means that this remaining variability in dose parameters is caused by inter-observer delineation variations and this should be taken into account when interpreting dose parameter data. Contouring of organs at risk on MRI scans would have been more precise than on CT-scans, but only a minority of centres have MRI available for standard cylinder-based brachytherapy.

Using a uniform protocol for VBT ensures high quality VBT and is essential for increasing reliability of dose parameters that can be used for evaluation of VBT related toxicity. A continuous QA-programme in a multi-institutional radiotherapy trial can increase treatment and delineation uniformity and which has been shown to impact on trial outcomes.[15, 32] A review on QA for radiotherapy in randomised trials showed that major protocol deviations were observed in 11.0-48.0% of all cases, and were reported to be associated with impaired overall survival and local control and potentially increased treatment related toxicity.[15] This has also been reported by several other investigators, emphasising that the design of the QA-procedure needs to be tailored to specific trial techniques and outcomes.[20, 22, 23, 32-34]

To our knowledge, this is the first study on dedicated QA for single channel VBT with delineation on CT- or MRI-scans for endometrial cancer. Our findings confirm that a dummy run and QA-procedure in multi-institutional radiotherapy trials creates awareness of the trial protocol and principles and guidelines of the specific treatment, improves protocol adherence and quality of the treatment. Even after successful initial dummy run procedures, annual QA showed major protocol deviations in 18.5% of reviewed cases, suggesting that continuous annual QA is essential to promote protocol adherence, ensuring uniform high-quality vaginal brachytherapy a multi-institutional trial.

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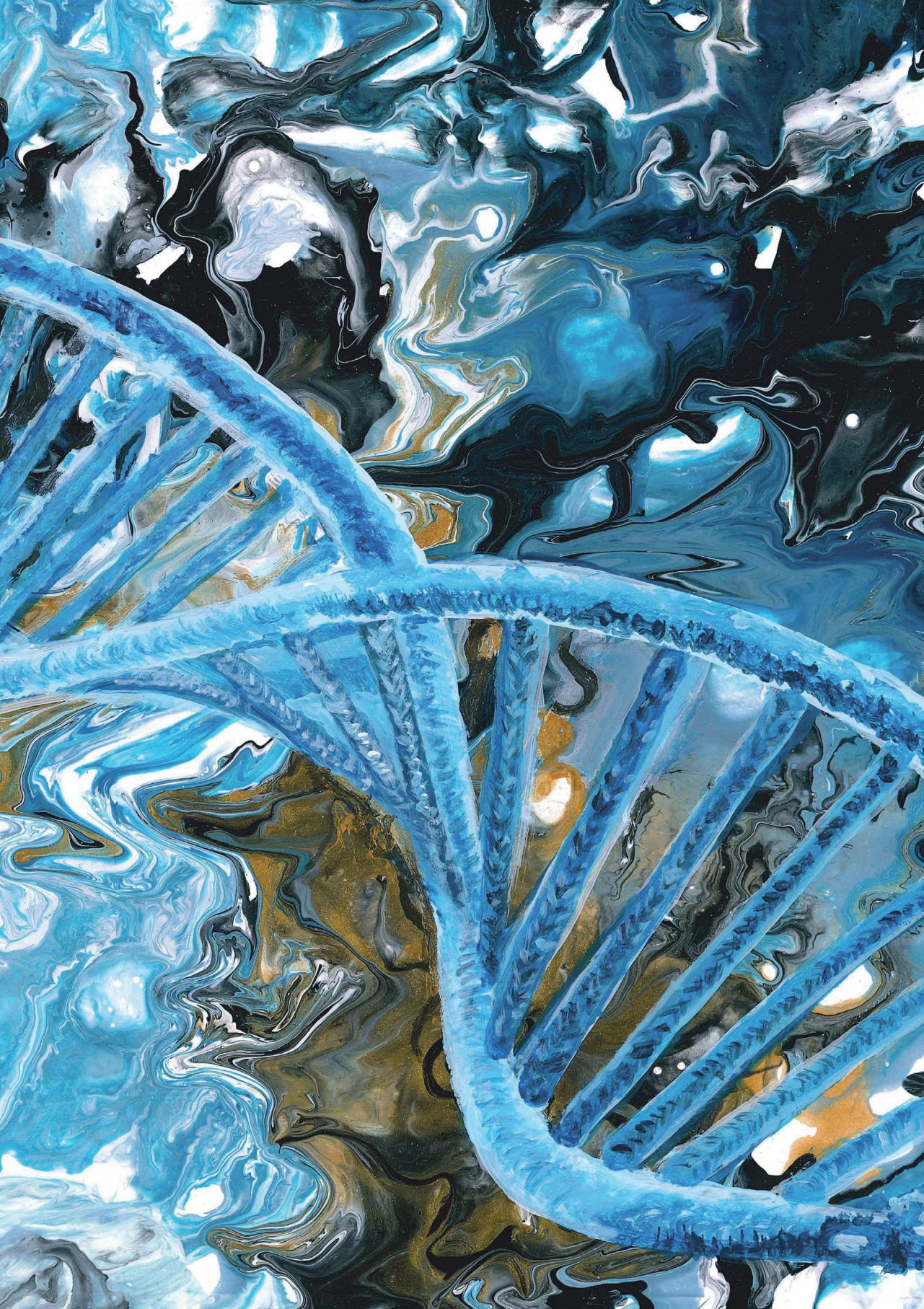
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CHAPTER 5

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 (HR-EC) 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 HR-EC 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 HR-EC, 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 (HR-EC). Women with HR-EC 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 HR-EC 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 HR-EC 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

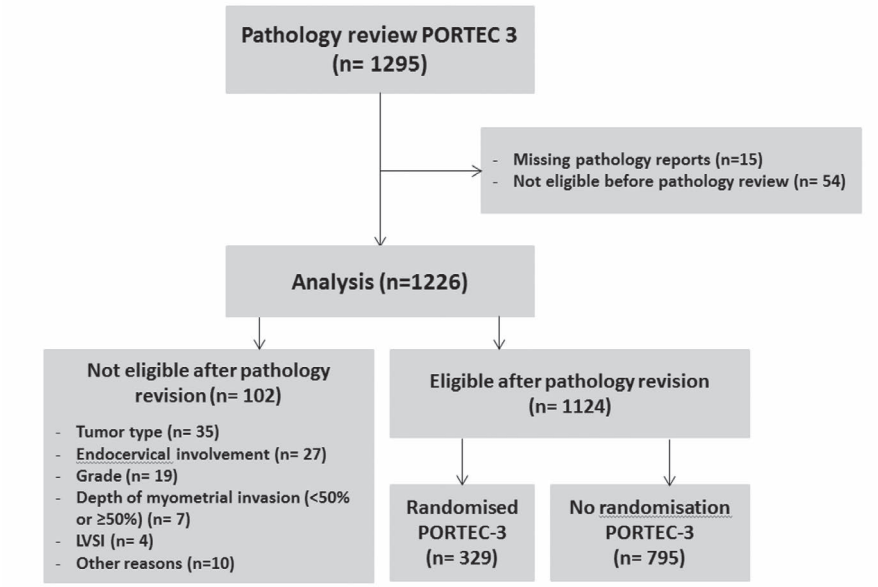
Each participating group had appointed expert gynaeco-pathologists as reviewers for the study. After surgery, the pathology diagnosis was made by the regional pathologist. In case of HR-EC, all histopathology slides and a copy of the pathology report were sent for pathology review as part of patient management, to confirm HR-EC within 1 week, with the aim to ensure that only true HR-EC 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 HR-EC and eligibility. For the randomised patients, the review report was completed after IC was given.

Figure 1. CONSORT diagram.



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 x^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, available at Annals of Oncology online).

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, available at Annals of Oncology online for results by country and supplementary Figure S1, available at Annals of Oncology online. Lowest inter-observer variability was 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.

Table 1. Major pathology criteria of the eligible patients (n=1226). The pathology criteria of the NL versus the UK patients were based on review pathology.

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	
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.

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

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

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

Total cohort

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
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.

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

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

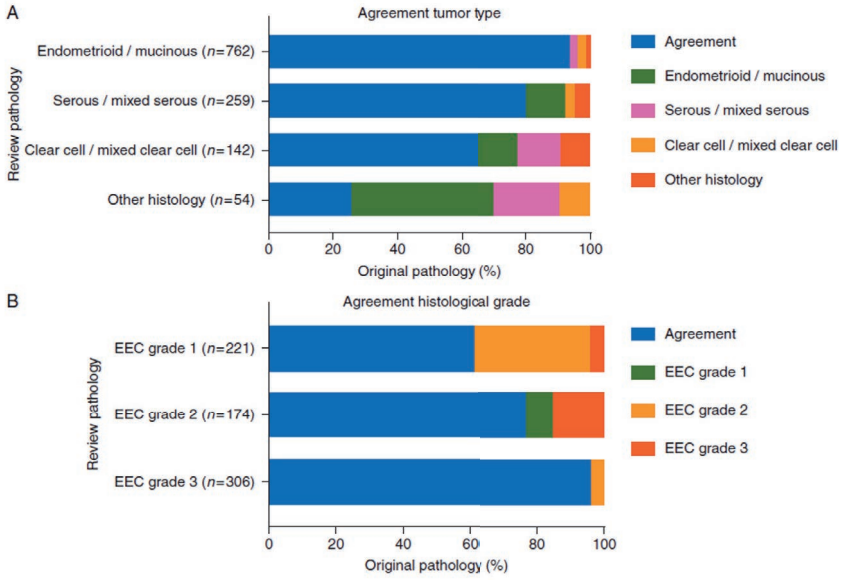
Pathology variables	cohort (n=102)		NL cohort (n=42)		UK cohort (n=60)	
	N	%	N	%	N	%
Histological type	35	34%	14	33%	21	35%
Histologic grade#	19	19%	7	17%	12	20%
Myometrial invasion	7	7%	3	7%	4	7%
Cervical involvement	27	27%	12	29%	15	25%
LVSI	4	4%	2	5%	2	3%
Other±	10	10%	4	10%	6	10%
Total ineligible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

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

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.



DISCUSSION

In the PORTEC-3 trial of adjuvant RT with or without chemotherapy for women with HR-EC, upfront pathology review was carried out before patient counselling to ensure that only true HR-EC patients were informed about the trial, and that the trial only enrolled true HR-EC 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 HR-EC 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, available at Annals of Oncology online). 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 HR-EC 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 DATA

Appendix 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
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. Abbreviations: FIGO: International Federation of Gynecology and Obstetrics; LVSI: lymph-vascular space invasion; EEC: endometrioid endometrial cancer; NEEC: non-endometrioid endometrial cancer; * other histology includes undifferentiated, other mixed combinations

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

NL cohort

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
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

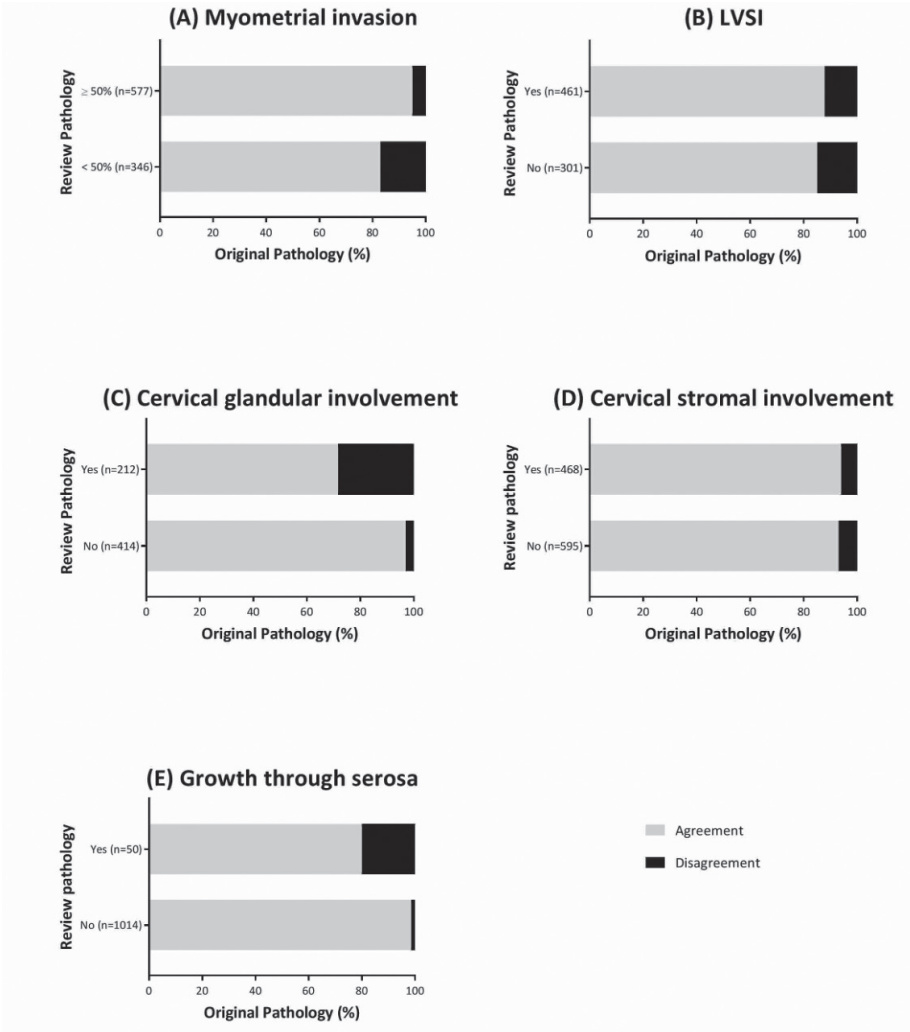
UK cohort

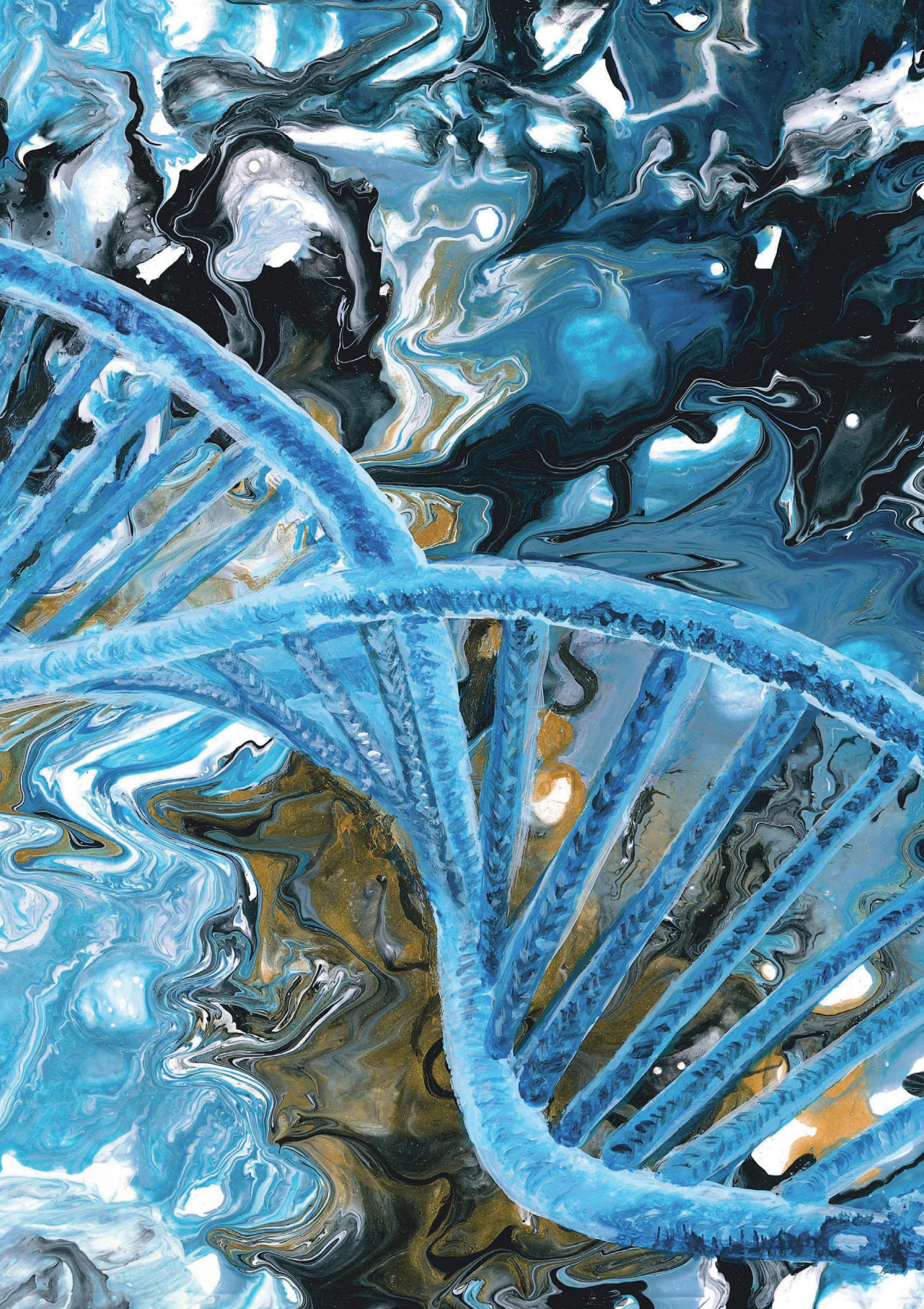
Pathology item	Total number available for analysis*	Missing items	Total discrepancies	Disagreement % #	Leading to ineligibility	Leading to ineligibility % $	Not leading to ineligibility	Not leading to ineligibility % ¥	Kappa value
Histological type	849	9	127	15%	21	17%	106	83%	0.74
Histological grade (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 (including serosal breach)	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.

Abbreviations: 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 6

RADIOTHERAPY TECHNIQUES AND TREATMENT-RELATED TOXICITY IN THE PORTEC-3 TRIAL: COMPARISON OF THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY VERSUS INTENSITY-MODULATED RADIOTHERAPY

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ABSTRACT

Purpose: Radiation therapy techniques have developed from 3-dimensional conformal radiation therapy (3DCRT) to intensity modulated radiation therapy (IMRT), with better sparing of the surrounding normal tissues. The current analysis aimed to investigate whether IMRT, compared to 3DCRT, resulted in fewer adverse events (AEs) and patient-reported symptoms in the randomized PORTEC-3 trial for high-risk endometrial cancer.

Methods and Materials: Data on AEs and patient-reported quality of life (QoL) of the PORTEC-3 trial were available for analysis. Physician-reported AEs were graded using Common Terminology Criteria for Adverse Events v3.0. QoL was assessed by the European Organisation for Research and Treatment of Cancer QLQC30, CX24, and OV28 questionnaires. Data were compared between 3DCRT and IMRT. A P value of $\leq .01$ was considered statistically significant due to the risk of multiple testing. For QoL, combined scores 1 to 2 ("not at all" and "a little") versus 3 to 4 ("quite a bit" and "very much") were compared between the techniques.

Results: Of 658 evaluable patients, 559 received 3DCRT and 99 IMRT. Median follow-up was 74.6 months. During treatment no significant differences were observed, with a trend for more grade $\geq$3 AEs, mostly hematologic and gastrointestinal, after 3DCRT (37.7% vs 26.3%, P = .03). During follow-up, 15.4% (vs 4%) had grade $\geq$2 diarrhea, and 26.1% (vs 13.1%) had grade $\geq$2 hematologic AEs after 3DCRT (vs IMRT) (both $P < .01$). Among 574 (87%) patients evaluable for QoL, 494 received 3DCRT and 80 IMRT. During treatment, 37.5% (vs 28.6%) reported diarrhea after 3DCRT (vs IMRT) (P = .125); 22.1% (versus 10.0%) bowel urgency (P = .039), and 18.2% and 8.6% abdominal cramps (P = .058). Other QoL scores showed no differences.

Conclusions: IMRT resulted in fewer grade $\geq$3 AEs during treatment and significantly lower rates of grade $\geq$2 diarrhea and hematologic AEs during follow-up. Trends toward fewer patient-reported bowel urgency and abdominal cramps were observed after IMRT compared to 3DCRT.

INTRODUCTION

Over the last decades, radiation therapy techniques have developed from parallel opposing fields or 2-dimensionally planned radiation therapy to 3- and 4-field techniques and to 3- dimensional conformal radiation therapy (3DCRT). More recent developments are 3- dimensional image guided intensity modulated radiation therapy (IMRT) and volumetric modulated arc radiation therapy (VMAT). With IMRT and VMAT, the radiation dose is delivered more conformally to the target volume and the dose to the adjacent organs at risk (OARs) is reduced, compared to 3DCRT, without compromising clinical outcome.[1-6] With the introduction of more advanced radiation therapy techniques, it is expected that treatment-related adverse events (AEs) for pelvic radiation therapy can be reduced.

Multiple retrospective studies and 2 prospective randomized trials have shown that intensity modulated techniques significantly reduce treatment-related acute and late AEs and patient-reported symptoms in women with endometrial or cervical cancer.[5-12] However, limitations of most studies were small numbers of patients, retrospective data collection, limited follow-up, or lack of data on patient-reported symptoms.

The randomized PORTEC-3 trial investigated radiation therapy versus chemoradiation therapy for women with high-risk endometrial cancer (EC) and showed that radiation therapy combined with concurrent and adjuvant chemotherapy improved overall and failure-free survival.[13] Analyses of acute AEs showed that pelvic radiation therapy was associated with mostly gastrointestinal acute AEs of mild to moderate severity and that the addition of chemotherapy resulted in added hematologic and neurologic AEs.[14,15] Within the PORTEC-3 trial, 68.5% (94.2% chemoradiation therapy vs 43.2% radiation therapy alone) had any grade ≥2 AEs during treatment, and 44.3% and 43.8% of all patients experienced grade ≥2 gastrointestinal and hematologic AEs, respectively. Persistent grade ≥2 AEs, up to 5 years after treatment, were observed for 31%, with 7.3% gastrointestinal and 2.5% hematologic AEs.[15,16]

In the PORTEC-3 trial, the standard radiation technique used at the time was 3DCRT, but IMRT was allowed if standard for the center and with adequate quality assurance (QA). The aim of the current study was to investigate whether use of IMRT in the PORTEC-3 trial was associated with reduced physician-reported AEs and fewer patient-reported symptoms.

METHODS AND MATERIALS

Study design and patient selection of the PORTEC-3 trial

The international, randomized PORTEC-3 trial was designed to investigate the benefit of external beam radiation therapy with concurrent and adjuvant chemotherapy (chemoradiation therapy)

compared to radiation therapy alone in women with high-risk EC. Inclusion criteria for the trial were endometrioid-type EC, Federation of Gynecology and Obstetrics 2009 stage I, grade 3, with myometrial invasion and lymphovascular space invasion; stage II; stage IIIA; stage IIIB (parametrial invasion only) or stage IIIC; and serous or clear cell type EC stage IA (with invasion) to III. Primary endpoints of the trial were overall survival and failure-free survival; secondary endpoints included physician-reported AEs, patient-reported quality of life (QoL), and pelvic or distant relapse. More detailed information on patient selection, treatment, and outcomes has been reported in previous publications.[13, 15, 16]

Procedures

All women underwent surgery that consisted of total abdominal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy, with or without lymph node dissection. After surgery, they were randomized 1:1 to either pelvic external beam radiation therapy alone or concurrent chemotherapy and pelvic radiation therapy, administered with a total dose of 45.0 to 50.4 Gy with a recommended dose of 48.6 Gy in 1.8 Gy daily fractions 5 times a week. A vaginal brachytherapy boost was indicated in case of cervical stromal involvement. The clinical target volume for external beam radiation therapy consisted of the proximal half of the vagina; the parametrial tissues; pelvic lymph nodes; and internal, external, and common iliac lymph node regions up to the upper level of S1. It was extended in case lymph nodes were involved. The planning target volume consisted of the CTV with a 7 to 10 mm margin. Standard technique was computed tomography–based 3DCRT (four-field "box" technique with or without supplementary fields or segments), according to the ICRU-50 recommendations. IMRT, with similar margins, was allowed when centers had sufficient clinical experience with pelvic IMRT and had arranged adequate local QA procedures as dose verification and daily cone-beam computed tomography. Radiation therapy QA was initially not included in the trial, but was added later by the Trans-Tasman Radiation Oncology Group. The QA procedure for centers of the Australia and New Zealand Gynaecologic Oncology Group consisted of a benchmarking exercise before participation in the trial and regular QA thereafter; for international sites, an independent retrospective review of a single radiation therapy plan of each participating center was conducted.[17]

Treatment should preferably start within 4 to 6 weeks, but no later than 8 weeks, from surgery. In the chemoradiation therapy arm, patients received 2 cycles of cisplatin the first and fourth week of radiation therapy, and 4 cycles of 3-weekly carboplatin and paclitaxel after completion of radiation therapy.

Adverse events and quality of life assessment

Physician-reported AEs were assessed by the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 at baseline (after surgery), after completion of the radiation therapy, at each

cycle of adjuvant chemotherapy, at a 6-month interval until 5 years, and at 7 and 10 years from randomization. For the QoL assessment, a questionnaire including the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) version 3.0, the cervix module (CX-24), and subscales for neuropathy and chemotherapy symptoms from the ovarian module (OV-28) were used.[18] For the single items, symptom scores between 1 and 4 were recorded, with 1 being no symptoms ("not at all"), 2 "a little," 3 "quite a bit," and 4 "very much" for each symptom.

Questionnaires were filled out at baseline after surgery, after completion of radiation therapy, every 6 months until 2 years, and thereafter at 3 and 5 years from randomization.[15, 16]

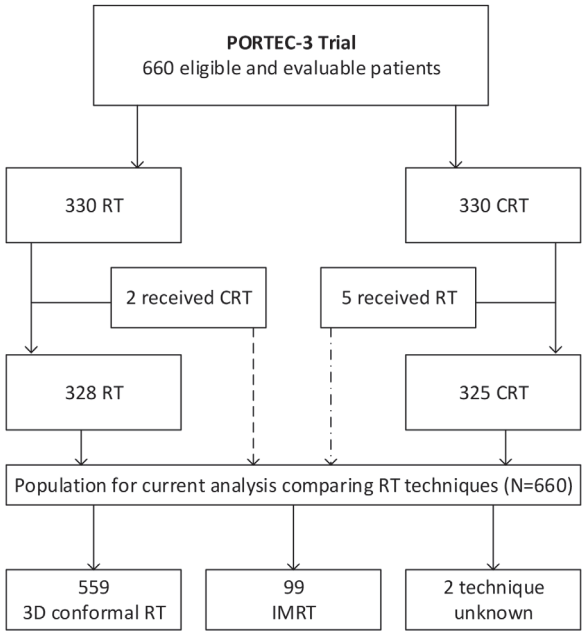
Statistical design

Statistical analyses were performed with SPSS, version 25.0 (SPSS, Inc., Chicago, IL). All patients were evaluable for analysis of physician-reported AEs. Patients who filled in the baseline and at least 1 follow-up questionnaire were included in the QoL analysis. Patients did not receive further QoL questionnaires after being diagnosed with a recurrence; however, all data, up to the date of a recurrence, were included in the analysis.

To compare patient and tumor characteristics between the 2 radiation techniques $\chi 2$ statistics or Fisher's exact test for categorical variables and t test for continuous variables were used (significance P value $<.05$). Physician-reported AEs were calculated at each timepoint (using the maximum grade scored) and compared between the radiation therapy techniques by the Fisher exact test.

The timepoint "during treatment" consisted of all AE forms related to radiation therapy and concurrent and adjuvant chemotherapy and the timepoint "during follow-up" of all AE forms collected during the entire follow-up period. For these timepoints, the maximum grade was used as a summary of toxicity. QoL analysis was done according to the EORTC Quality of Life Group guidelines.[18] A linear mixed model was used to obtain estimates for the EORTC QLQ-C30, CX24, and OV28 subscales at each of the timepoints, with patient as random effect and time (categorical), technique, and their interaction as fixed effects. Single items were compared by using generalized mixed models binary logistic regression with the same random and fixed effects as the linear mixed model, with combined scores 1 to 2 ("not at all" and "a little") and 3 to 4 ("quite a bit" and "very much"). Missing data were handled as missing at random. A P value of $\leq .01$ was considered statistically significant to prevent false-positive results due to multiple testing.

Figure 1. Flowchart of the PORTEC-3 trial.



RT: Radiotherapy; CRT: Chemoradiotherapy; IMRT: Intensity-modulated radiotherapy.

RESULTS

Study population

Between September 15, 2006, and December 20, 2013, 660 eligible and evaluable patients were included in the PORTEC-3 trial. Of these patients, 333 received radiation therapy and 327 received chemoradiation therapy; 559 (85.0%) received 3DCRT; 99 (15.0%) patients received IMRT; and for 2 patients, the type of technique was unknown (Fig. 1). 3DCRT consisted of 3-field, 4-field, or multiple-field radiation therapy techniques. IMRT was used in 42 of 103 participating centers and typically consisted of 7 static fields with multiple segments (Fig. E1). Median follow-up at the time of analysis was 74.6 months. Patient characteristics by initial treatment arm and technique are displayed in Table 1and showed no significant differences. IMRT and 3DCRT were used equally in both initial treatment arms (Table 1). Radiation therapy target areas (pelvic vs pelvic and paraortic region) did not differ significantly between the 2 techniques, with only 38 patients receiving paraortic radiation therapy. Of all patients, 574 (87.0%) patients were evaluable for QoL, of whom 493 (85.9%) received 3DCRT and 80 (13.9%) IMRT; for 1 patient, the technique was unknown (0.2%). The completion rate of the QoL questionnaire was 89.4% at 3 years and 62.8% at 5 years.

Physician-reported adverse events

At baseline, no significant differences in frequency and grades of AEs were observed between the radiation therapy techniques. Specifically, 226 of 559 patients (40.4%) and 41 of 99 (41.4%) patients had any grade ≥2 AE at baseline (after surgery); 57 of 559 (10.2%) and 4 of 99 (4.0%) any grade ≥3 AE (P = .92 and P = .06, respectively).

The most frequent AEs during treatment were gastrointestinal (43.6%), hematologic (43.3%), and pain (24.0%). No significant differences were found between the radiation therapy techniques, and a trend for more grade ≥3 AEs was observed with 3DCRT (37.7% vs 26.3% for IMRT, P = 0.03) (see Table 2 and Fig. 2). At 6 months, 274 of 560 (48.9%) patients who had been treated with 3DCRT had any grade ≥2 AE versus 29 of 97 (29.9%) of those who had received IMRT (P < .01). Grade ≥2 hematologic AEs were reported for 104 of 560 (18.6%) and 7 of 97 (7.2%) patients (P < .01). During follow-up, 443 of 559 (79.2%) versus 67 of 99 (67.7%) patients had any grade ≥2 AE (P = .01), of whom 78 (13.9%) versus 4 (4.0%) had grade ≥2 diarrhea and 143 (25.6%) versus 13 (13.1%) any grade ≥2 hematologic AE, respectively (both P < .01) (Table E1). A total of 176 (31.5%) versus 21 (21.2%) patients had any grade ≥3 AE during follow-up (P = .04) (Table E1). At 1, 2, and 3 years, no significant differences were recorded. At 5 years, significantly more grade ≥2 AEs were observed after 3DCRT (33.5% vs 14.6%, P < .01), but toxicity data were only available for 60% of patients at this time point. No significant differences were recorded for genitourinary AEs.

Table 1. Patient characteristics.

	PORTEC-3 population by technique (n = 658)			PORTEC-3 population by arm (n = 660)	
	IMRT (n = 99)	Conformal RT (n = 559)	*P value*	CRT (n = 327)	RT (n = 333)
Age at randomization, y					
Median	62.2 (56.1-68.1)	62.9 (56.5-68.0)	.24	61.9 (55.9-68.1)	62.5 (56.5-68.0)
<60	34 (34.3%)	232 (41.5%)	-	127 (38.8%)	141 (42.3%)
60-69	48 (48.5%)	224 (40.1%)	-	142 (43.4%)	130 (39.0%)
≥70	17 (17.2%)	103 (18.4%)	-	58 (17.7%)	62 (18.6%)
WHO					
0-1	95 (96,9%)	550 (98.7%)	0.18	320 (98.5%)	327 (98.5%)
2	3 (3.1%)	7 (1.3%)	-	5 (1.5%)	5 (1.5%)
Unknown	1	2		2	1
Comorbidity					
Diabetes	8 (8.1%)	73 (13.1%)	.33	45 (13.8%)	36 (10.8%)
Hypertension	36 (36.4%)	184 (33.0%)	.49	115 (35.2%)	105 (31.6%)
Cardiovascular	10 (10.2%)	39 (7.0%)	.50	29 (9.0%)	20 (6.0%)
FIGO					
Ia	10 (10.1%)	67 (12.0%)	.30	39 (11.9%)	39 (11.7%)
Ib	13 (13.1%)	103 (18.4%)	-	58 (17.7%)	59 (17.7%)
II	28 (28.3%)	142 (25.4%)	-	79 (24.2%)	91 (27.3%)
III	48 (48.5%)	247 (44.2%)	-	151 (46.2%)	144 (43.2%)
Histology					
Endometrioid	72 (72.7%)	398 (71.2%)	.27	234 (70.9%)	237 (71.8%)
Serous	13 (13.1%)	92 (16.5%)	-	53 (16.1%)	52 (15.8%)
Clear cell	8 (8.1%)	53 (9.5%)	-	29 (8.7%)	33 (10.0%)
Other	6 (6.1%)	16 (2.9%)	-	14 (4.3%)	8 (2.4%)
Type of surgery					
TAH-BSO	29 (29.3%)	164 (29.3%)	.96	96 (29.4%)	98 (29.4%)
TAH-BSO with LND/ full staging	39 (39.4%)	234 (41.9%)	-	140 (42.8%)	133 (39.9%)
TLH-BSO	14 (14.1%)	72 (12.9%)	-	44 (13.5%)	43 (12.9%)
TLH-BSO with LND/full staging	17 (17.2%)	89 (15.9%)	-	47 (14.4%)	59 (17.7%)
Treatment					
Chemoradiation arm	53 (53.5%)	273 (48.8%)	0.69	327 (100%)	-
Radiation therapy arm	46 (46.5%)	286 (51.2%)	-	-	333 (100%)
Brachytherapy boost	48 (48.5%)	261 (46.7%)	0.73	149 (45.6%)	160 (48.0%)
Radiation therapy technique					
IMRT	99 (100%)	-	-	53 (16.2%)	46 (13.8%)
Conformal RT	-	559 (100%)	-	273 (83.5%)	286 (85.9%)

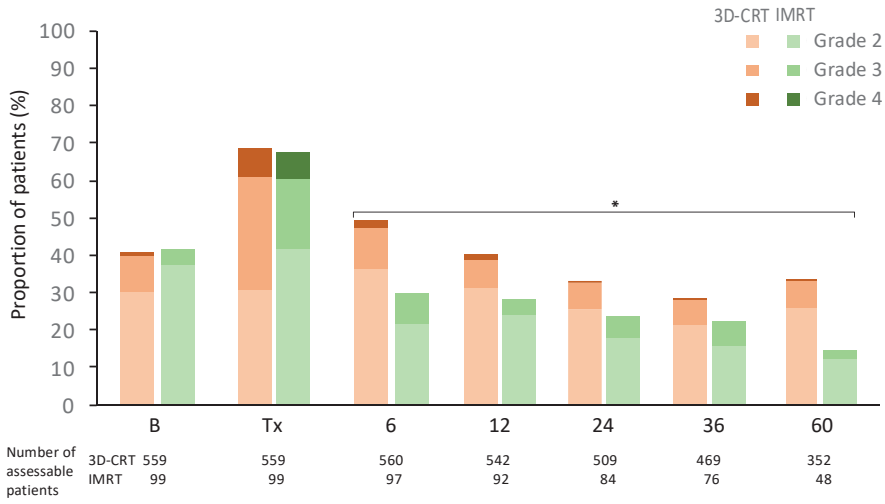
Abbreviations: CRT = chemoradiation therapy; IMRT = intensity modulated radiation therapy; LND = lymph node dissection; RT = radiation therapy; TAH-BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy; TLH = total laparoscopic hysterectomy.

Table 2. Physician-reported toxicity during treatment, at 6 months and at 3 years by radiotherapy technique.

	During treatment						At 6 months						At 3 years					
	Grade 2		P*	Grade 3-4		P	Grade 2		P*	Grade 3-4		P	Grade 2		P*	Grade 3-4		P
	IMRT (n = 99)	3DCRT (n = 559)		IMRT (n = 99)	3DCRT (n = 559)		IMRT (n = 97)	3DCRT (n = 560)		IMRT (n = 97)	3DCRT (n = 560)		IMRT (n = 76)	3DCRT (n = 469)		IMRT (n = 76)	3DCRT (n = 469)	
Any	41 (41%)	172 (31%)	0.91	26 (26%)	211 (38%)	0.03	21 (22%)	203 (36%)	<0.01	8 (8%)	71 (13%)	.24	12 (16%)	99 (21%)	0.33	5 (7%)	33 (7%)	1.00
Any grade 3	-	-		19 (19%)	168 (30%)		-	-		8 (8%)	62 (11%)		-	-		5 (7%)	32 (7%)	
Any grade 4	-	-		7 (7%)	43 (8%)		-	-		0 (0%)	9 (2%)		-	-		0 (0%)	1 (<1%)	
Gastrointestinal, any	38 (38%)	185 (33%)	1.00	5 (5%)	59 (11%)	.09	5 (5%)	32 (6%)	0.55	1 (1%)	15 (3%)	.49	5 (7%)	23 (5%)	0.42	1 (1%)	2 (<1%)	.36
Diarrhea	29 (29%)	141 (25%)	0.91	3 (3%)	45 (8%)	.09	1 (1%)	18 (3%)	0.23	0 (0%)	3 (1%)	1.00	2 (3%)	10 (2%)	1.00	0 (0%)	2 (<1%)	1.00
Nausea	14 (14%)	78 (14%)	1.00	1 (1%)	10 (2%)	1.00	2 (2%)	10 (2%)	1.00	0 (0%)	7 (1%)		0 (0%)	1 (<1%)	1.00	0 (0%)	0 (0%)	1.00
Vomiting	5 (5%)	35 (6%)	0.83	1 (1%)	4 (1%)	.56	1 (1%)	12 (2%)	0.49	0 (0%)	3 (1%)		0 (0%)	1 (<1%)	1.00	0 (0%)	0 (0%)	1.00
Constipation	3 (3%)	35 (6%)	0.25	0 (0%)	1 (<1%)	1.00	2 (2%)	9 (2%)	1.00	0 (0%)	3 (1%)	1.00	1 (1%)	5 (1%)	0.60	0 (0%)	0 (0%)	1.00
Ileus/obstruction	2 (2%)	6 (1%)	0.40	1 (1%)	3 (1%)	.48	0 (0%)	2 (<1%)	0.49	1 (1%)	14 (3%)	.71	0 (0%)	0 (0%)	0.14	1 (1%)	0 (0%)	.14
Genitourinary																		
Dysuria	8 (8%)	24 (4%)	1.00	1 (1%)	0 (0%)	.15	0 (0%)	8 (1%)	0.61	0 (0%)	0 (0%)	1.00	1 (1%)	3 (1%)	0.45	0 (0%)	0 (0%)	1.00
Urinary frequency/ urgency	5 (5%)	29 (5%)	0.82	0 (0%)	4 (1%)	1.00	1 (1%)	10 (2%)	1.00	0 (0%)	0 (0%)	1.00	0 (0%)	12 (3%)	0.39	0 (0%)	0 (0%)	1.00
Incontinence	2 (2%)	15 (3%)	1.00	0 (0%)	1 (<1%)	1.00	1 (1%)	12 (2%)	0.71	0 (0%)	1 (<1%)	1.00	0 (0%)	11 (2%)	0.39	0 (0%)	1 (0%)	1.00
Pain, any	19 (19%)	104 (19%)	1.00	5 (5%)	30 (5%)	1.00	6 (6%)	57 (10%)	0.22	1 (1%)	9 (2%)	1.00	6 (8%)	26 (6%)	0.62	0 (0%)	4 (1%)	1.00
Muscle pain	8 (8%)	45 (8%)	1.00	1 (1%)	8 (1%)	1.00	0 (0%)	6 (1%)	0.60	0 (0%)	0 (0%)	1.00	0 (0%)	3 (1%)	1.00	0 (0%)	0 (0%)	1.00
Arthralgia	7 (7%)	46 (8%)	0.71	1 (1%)	9 (2%)	1.00	1 (1%)	13 (2%)	1.00	1 (1%)	0 (0%)	.15	1 (1%)	6 (1%)	1.00	0 (0%)	1 (<1%)	1.00
Back/pelvic/limbs	4 (4%)	10 (2%)	0.57	1 (1%)	10 (2%)	1.00	2 (2%)	17 (3%)	1.00	1 (1%)	2 (<1%)	.38	1 (1%)	6 (1%)	1.00	0 (0%)	1 (<1%)	1.00
Abdomen/cramps	5 (5%)	18 (3%)	0.61	1 (1%)	7 (1%)	1.00	3 (3%)	11 (2%)	0.75	0 (0%)	5 (1%)	1.00	3 (4%)	3 (1%)	0.06	0 (0%)	1 (<1%)	1.00
Musculoskeletal	1 (1%)	3 (1%)	1.00	0 (0%)	2 (<1%)	1.00	0 (0%)	2 (<1%)	1.00	0 (0%)	0 (0%)	1.00	0 (0%)	1 (<1%)	1.00	0 (0%)	1 (<1%)	1.00
Fatigue	16 (16%)	59 (11%)	0.33	0 (0%)	10 (2%)	.37	2 (2%)	10 (2%)	0.45	1 (1%)	1 (<1%)	.27	1 (1%)	0 (0%)	0.14	0 (0%)	0 (0%)	1.00
Neuropathy, any	12 (12%)	70 (13%)	0.46	1 (1%)	22 (4%)	0.23	3 (3%)	40 (7%)	0.55	3 (3%)	7 (1%)	.17	2 (3%)	17 (4%)	1.00	1 (1%)	2 (<1%)	.36
Motor	0 (0%)	14 (3%)	0.09	0 (0%)	4 (1%)	1.00	0 (0%)	8 (1%)	0.70	1 (1%)	4 (1%)	.55	2 (3%)	3 (1%)	0.20	0 (0%)	1 (<1%)	1.00
Sensory	12 (12%)	66 (12%)	0.65	1 (1%)	21 (4%)	0.23	3 (3%)	38 (7%)	0.52	2 (2%)	4 (1%)	.22	2 (3%)	16 (3%)	1.00	1 (1%)	2 (<1%)	.36
Hematological, any	16 (16%)	103 (18%)	0.23	21 (21%)	145 (26%)	0.38	2 (2%)	79 (14%)	<0.01	5 (5%)	25 (4%)	.79	0 (0%)	6 (1%)	1.00	1 (1%)	2 (<1%)	.36
Lymphatics (edema)	1 (1%)	10 (2%)	0.70	0 (0%)	2 (<1%)	1.00	4 (4%)	7 (1%)	0.09	0 (0%)	1 (<1%)	1.00	0 (0%)	4 (1%)	1.00	0 (0%)	2 (<1%)	1.00
Hypertension	4 (4%)	27 (5%)	0.49	0 (0%)	9 (2%)	0.37	4 (4%)	29 (5%)	0.38	0 (0%)	10 (2%)	.37	3 (4%)	29 (6%)	0.25	0 (0%)	11 (2%)	.38

Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; RT = radiation therapy.
The maximum grade per patient per adverse event is shown.
* *P* values show significance for grade 2-4 adverse events.
Events at 1 and 2 years were similar to 3 years and therefore are not shown.

Figure 2. Incidence of the maximum physician-reported adverse event grades per patient for each timepoint in months at baseline, during and after 3-dimensional conformal radiation therapy and intensity modulated radiation therapy.

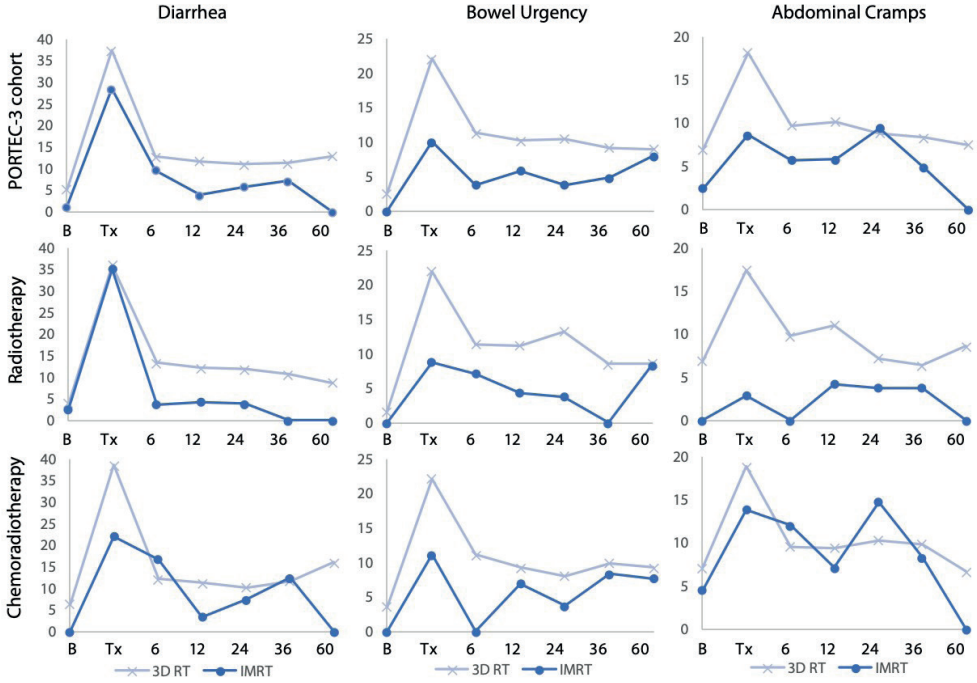


Abbreviations: B = baseline; 3DRT = 3-dimensional radiation therapy; IMRT = intensity modulated radiation therapy; Tx = during treatment (time in months) * significant difference.

Patient-reported symptoms on the QoL questionnaires

During treatment, the most common symptoms scored as “quite a bit” or “very much” were urinary frequency (40.3%), diarrhea (33.1%), and fatigue (32.1%), without significant differences between the radiation therapy techniques (Table 3). Trends were observed for more bowel urgency and abdominal cramps during treatment for those who received 3DCRT (22.1% vs 10.0% for IMRT [P = .039] and 18.2% vs 8.6% [P = .058]) (Fig. 3). Among genitourinary symptoms, urinary frequency differed significantly over time, without significant differences between the techniques at fixed timepoints (Table 3) (Fig. E2). At 6 months, 12.7% versus 9.6%, 11.3% versus 3.8%, and 9.7% versus 5.7% of patients (P = .670, P = .170, and P = .316, respectively) who had been treated with 3DCRT versus IMRT reported “quite a bit” to “very much” diarrhea, bowel urgency, and abdominal cramps. For patients who received radiation therapy only, these percentages were 13.3% versus 3.6%, 22.0% versus 8.8%, and 17.5% versus 2.9% (P = .158, P = .390, and P = .996, respectively). At 1, 2, and 3 years, no significant differences were observed in gastrointestinal and genitourinary symptoms between the 2 techniques. Development over time of other symptoms, such as lower back and muscle and joint pain, differed significantly by technique, without differences between the techniques at fixed timepoints (Table 3 and Fig. E2). Vaginal and sexual symptoms did not differ between the 2 techniques. Physical functional scales did not differ between 3DCRT and IMRT.

Figure 3. Percentage of patients who reported "quite a bit" or "very much" of diarrhea, bowel urgency or abdominal cramps in the total PORTEC-3 cohort, during and after radiation therapy only and after chemoradiation therapy.



Abbreviations: B = baseline; 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; Tx = during treatment (time in months).

DISCUSSION

This analysis of radiation therapy techniques in the PORTEC-3 trial showed that IMRT, compared to 3DCRT, was associated with lower rates of grade ≥3 AEs, mostly gastrointestinal and hematologic, during treatment. Furthermore, IMRT significantly reduced grade ≥2 AEs and grade ≥2 diarrhea and hematologic AEs during follow-up. Analysis of patient-reported QoL showed trends toward a reduced symptom burden with lower scores for diarrhea, bowel urgency, and abdominal cramps after IMRT versus 3DCRT. These findings support the rationale that women with high-risk EC should be treated with modern techniques such as IMRT or VMAT.

Table 3. Percentage of patients who reported symptoms scored as "quite a bit" or "very much" by radiation technique.

									P value						
		Baseline	Tx	6 mo	12 mo	24 mo	36 mo	60 mo	Technique	Time	Techn × time	Tx	6 mo	3 y	5 y
Gastro-intestinal															
Diarrhea	IMRT	1.2	28.6	9.6	3.8	5.7	7.1	0.0	.385	<.001	.018	.125	.670	.344	.891
	3DCRT	5.2	37.5	12.7	11.7	11.0	11.2	12.9							
Rectal bleeding	IMRT	0.0	1.4	0.0	0.0	1.9	0.0	0.0	.999	.999	.999	.666	.999	.999	.999
	3DCRT	0.6	0.7	1.0	0.3	1.4	0.3	0.5							
Bowel urgency	IMRT	0.0	10.0	3.8	5.8	3.8	4.8	8.0	.535	.812	.011	.039	0.170	0.390	0.731
	3DCRT	2.6	22.1	11.3	10.2	10.5	9.2	9.0							
Abdominal cramps	IMRT	2.4	8.6	5.7	5.8	9.4	4.8	0.0	.498	.543	.965	.058	0.316	0.311	0.933
	3DCRT	7.0	18.2	9.7	10.2	8.8	8.3	7.5							
Flatulence	IMRT	10.7	13.2	30.2	24.5	9.4	19.0	12.5	.149	.043	.075	.152	0.244	0.886	0.708
	3DCRT	15.3	20.6	20.8	20.7	21.7	18.9	19.6							
Genitourinary															
Urinary frequency	IMRT	26.2	44.3	20.8	22.6	19.2	28.6	8.0	.369	.001	.283	.285	0.912	0.594	0.028
	3DCRT	21.9	36.3	19.5	23.0	18.8	21.7	27.5							
Dysuria	IMRT	3.6	15.7	1.9	1.9	3.8	4.8	0.0	.873	.031	.543	.872	0.572	0.304	0.937
	3DCRT	5.2	16.1	2.6	2.6	1.4	1.9	1.9							
Urinary incontinence	IMRT	1.2	2.9	7.5	7.5	7.5	14.3	0.0	.980	.389	.001	.486	0.913	0.829	0.990
	3DCRT	3.8	6.0	6.5	8.4	9.6	12.8	11.8							
Difficulty emptying bladder	IMRT	6.0	5.7	3.8	3.8	5.7	7.1	4.0	.960	.993	.996	.759	0.384	0.490	0.781
	3DCRT	3.4	4.7	2.4	2.3	2.5	3.5	3.8							
Vaginal bleeding	IMRT	1.2	0.0	1.9	0.0	1.9	0.0	0.0	.995	.999	.999	.997	0.765	0.998	0.998
	3DCRT	0.8	1.0	1.3	1.0	0.3	0.3	0.5							
Vaginal dryness*	IMRT	0.0	21.4	16.7	20.0	16.7	33.3	25.0	.999	.984	.204	.837	0.772	0.946	0.808
	3DCRT	8.8	22.5	23.4	27.7	28.4	27.7	26.9							
Pain during sex*	IMRT	0.0	28.6	11.1	15.0	16.7	26.7	12.5	.998	.949	.246	.671	0.543	0.874	0.796
	3DCRT	2.8	21.2	17.5	16.4	17.9	18.8	19.7							
Other symptoms of interest															
Fatigue	IMRT	12.3	29.0	26.4	15.1	14.8	17.1	20.0	.767	.134	.687	.259	0.675	0.884	0.257
	3DCRT	17.9	35.1	23.8	17.4	18.2	18.9	12.9							
Nausea	IMRT	3.6	8.6	3.8	0.0	1.9	2.4	0.0	.966	.891	.977	.187	0.700	0.947	0.997
	3DCRT	3.4	14.6	5.4	3.8	3.9	2.9	4.7							
Vomiting	IMRT	1.2	1.4	0.0	0.0	1.9	0.0	0.0	.997	.999	.981	.566	0.998	0.998	0.999
	3DCRT	0.2	3.0	3.1	1.3	0.8	0.3	1.4							
Pain	IMRT	13.1	10.0	19.2	5.7	13.5	19.0	8.0	.380	.249	.375	.201	0.379	0.248	0.640
	3DCRT	10.0	14.1	16.6	14.8	13.5	13.1	10.4							
Lower back pain	IMRT	9.5	10.0	7.5	17.3	13.2	14.3	4.2	.424	.191	.001	.948	0.078	0.314	0.109
	3DCRT	10.0	9.0	17.4	16.5	18.3	19.4	19.6							
Muscle or joint pain	IMRT	6.0	22.1	32.7	29.4	24.0	28.6	13.6	.289	<.001	<.001	.129	0.492	0.110	0.900
	3DCRT	8.8	14.2	29.3	20.6	20.6	22.2	21.2							
Tingling or numbness	IMRT	0.0	1.4	22.6	26.9	11.3	16.7	8.0	.659	.040	<.001	.295	0.204	0.891	0.559
	3DCRT	1.8	5.0	30.8	22.4	16.7	18.4	18.5							

Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; Tx = during treatment.

* Only answered when sexually active.

Our study showed that IMRT resulted in fewer grade ≥3 AEs, mostly gastrointestinal, during treatment, which is consistent with findings of similar studies on the effect of IMRT for cervical cancer or EC on treatment-related acute AEs.[4, 5, 19] Aside from fewer grade ≥3 AEs, others reported fewer grade ≥2 gastrointestinal AEs during and directly after IMRT, but this could not be confirmed in the present study.[5, 9] We observed significantly fewer grade ≥2 AEs during follow-up, mainly diarrhea and hematologic AEs, for women who received IMRT compared to 3DCRT, even up to 5 years, which is in line with other reports on the long-term effects of IMRT versus 3DCRT for women with gynecologic malignancies.[5, 6, 10]

Patient-reported QoL did not differ significantly between the 2 radiation therapy techniques, although there were clear trends for fewer bowel symptoms such as cramps and urgency during and after IMRT. These trends seemed more obvious for women who received radiation therapy alone, but there was a slight imbalance at baseline in bowel symptoms favoring IMRT that could have influenced these trends. For women who received chemoradiation therapy a reduction of bowel symptoms was observed during treatment, but not during follow-up. Because 50% of patients in the PORTEC-3 trial received radiation therapy and 50% chemoradiation therapy and only 15.0% received IMRT, the number of patients was limited, and we were not able to draw conclusions on the interaction of RT techniques and treatment received. The results of the RTOG 1203 trial, which randomized women with endometrial or cervical cancer to either 3DCRT versus IMRT, showed significantly fewer bowel symptoms during and directly after IMRT compared to 3DCRT for women with endometrial and cervical cancer.[11, 12] This study used different QoL questionnaires compared to those in the present study, which makes it difficult to directly compare to our findings. Nevertheless, diarrhea, bowel urgency, and abdominal cramps seem to be prominent symptoms that were shown to be reduced with IMRT compared to 3DCRT in both the RTOG 1203 and the present study.

The lower rate of physician-reported AEs with IMRT for gynecologic malignancies has been related to reduced radiation doses to the small bowel, bladder, and rectum.[4, 5, 9, 10] Importantly, IMRT additionally spares pelvic bone marrow. Previous studies showed that reduced radiation dose to the pelvic bone marrow resulted in significant fewer hematologic AEs, which corresponds to the reduced grade ≥2 hematologic AEs with IMRT observed during follow-up in our study. Reduced hematologic AEs may lead to improved clinical outcomes by increasing tolerance for chemotherapy.[8, 20-22]

Limitations of the current study include it being a subanalysis of the PORTEC-3 trial that was not powered to detect a significant difference between the radiation therapy techniques. The relatively small number of patients who received IMRT and the lack of data on dosimetric parameters

and dose-volume histograms, which could have contributed to a better understanding of the reduced physician-reported AEs after IMRT, are further limitations. In addition, IMRT was still in its early phases during the accrual period, with ongoing introduction in many centers. Current standardized protocols with image guided radiation therapy, enabling smaller margins, and increased use of VMAT may result in even more normal tissue sparing and reduction of toxicities. Another limitation was the fact that toxicity and QoL data at 5 years were only available for approximately 60% of patients, and 5-year results should be interpreted with caution. Strengths of this study were the prospective data collection, including data on patient-reported QoL, the extensive follow-up period, and uniform radiation therapy treatment as described by the trial protocol.

For future perspectives, further reduction of morbidity can be expected by ongoing development and implementation of new radiation techniques. Imaging modalities with improved quality for image guided radiation therapy, such as magnetic resonance–guided radiation therapy and 4-dimensional cone-beam computed tomography, and automated treatment planning software provide the opportunity to further reduce unnecessary dose to OARs via smaller margins and daily adaptation to the target volume anatomy. These developments can lead to decreased treatment margins, increased precision, and decreased radiated OAR volume and thus reduced treatment-related AEs and patient-reported symptoms. Moreover, other radiation therapy modalities, such as proton beam radiation therapy, may further reduce dose to OARs, including bowel and bone marrow, even more, and the first studies are being initiated.[23-26] With these developments, the future of radiation therapy holds fewer AEs and increased QoL by more precise and image guided therapy with improvement of clinical outcomes.

CONCLUSIONS

Within the PORTEC-3 trial, IMRT resulted in fewer grade ≥3 AEs during treatment and significantly lower rates of grade ≥2 AEs, specifically diarrhea and hematologic AEs, during follow-up as compared to 3D-conformal radiation therapy. Trends toward fewer patient-reported bowel symptoms were observed after IMRT. Intensity-modulated techniques such as IMRT or VMAT should be the standard techniques for women receiving adjuvant radiation therapy for high-risk EC.

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SUPPLEMENTARY DATA

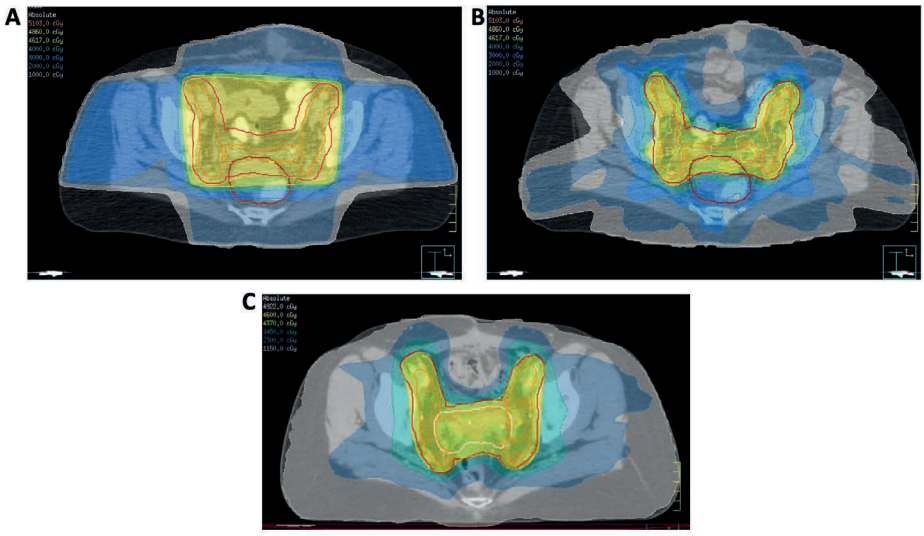
Table E1. Physician-reported toxicity during treatment and the follow-up period.

	During treatment						During follow-up					
	Grade 2		p*	Grade 3-4		p	Grade 2		p*	Grade 3-4		p
	IMRT (n=99)	3DCRT (n=559)		IMRT (n=99)	3DCRT (n=559)		IMRT (n=99)	3DCRT (n=599)		IMRT (n=99)	3DCRT (n=599)	
Any	41 (41%)	172 (31%)	0.91	26 (26%)	211 (38%)	0.03	46 (46%)	267 (48%)	0.01	21 (21%)	176 (31%)	0.04
Any grade 3	-	-		19 (19%)	168 (30%)					20 (20%)	151 (27%)	
Any grade 4	-	-		7 (7%)	43 (8%)					1 (1%)	25 (4%)	
Gastro-intestinal, any	38 (38%)	185 (33%)	1.00	5 (5%)	59 (11%)	0.09	18 (18%)	110 (20%)	0.27	4 (4%)	40 (7%)	0.38
- Diarrhea	29 (29%)	141 (25%)	0.91	3 (3%)	45 (8%)	0.09	4 (4%)	66 (12%)	<0.01	0 (0%)	12 (2%)	0.23
- Nausea	14 (14%)	78 (14%)	1.00	1 (1%)	10 (2%)	1.00	3 (3%)	21 (4%)	0.81	1 (1%)	8 (1%)	1.00
- Vomiting	5 (5%)	35 (6%)	0.83	1 (1%)	4 (1%)	0.56	1 (1%)	21 (4%)	0.10	0 (0%)	4 (1%)	1.00
- Constipation	3 (3%)	35 (6%)	0.25	0 (0%)	1 (<1%)	1.00	6 (6%)	33 (6%)	1.00	1 (1%)	6 (1%)	1.00
- Ileus/obstruction	2 (2%)	6 (1%)	0.40	1 (1%)	3 (1%)	0.48	4 (4%)	9 (2%)	0.34	2 (2%)	23 (4%)	0.41
Genitourinary												
- Dysuria	8 (8%)	24 (4%)	1.00	1 (1%)	0 (0%)	0.15	3 (3%)	16 (3%)	1.00	0 (0%)	1 (0%)	1.00
- Urinary frequency/urgency	5 (5%)	29 (5%)	0.82	0 (0%)	4 (1%)	1.00	8 (8%)	60 (11%)	0.40	1 (1%)	4 (1%)	1.00
- Incontinence	2 (2%)	15 (3%)	1.00	0 (0%)	1 (<1%)	1.00	7 (7%)	65 (12%)	0.19	0 (0%)	9 (2%)	0.37
Pain, any	19 (19%)	104 (19%)	1.00	5 (5%)	30 (5%)	1.00	28 (28%)	140 (25%)	0.73	2 (2%)	38 (7%)	0.07
- Muscle pain	8 (8%)	45 (8%)	1.00	1 (1%)	8 (1%)	1.00	0 (0%)	24 (4%)	0.02	0 (0%)	3 (1%)	1.00
- Arthralgia	7 (7%)	46 (8%)	0.71	1 (1%)	9 (2%)	1.00	5 (5%)	53 (9%)	0.27	1 (1%)	3 (1%)	0.48
- Back/pelvic/limbs	4 (4%)	10 (2%)	0.57	1 (1%)	10 (2%)	1.00	9 (9%)	50 (9%)	1.00	1 (1%)	9 (2%)	1.00
- Abdomen/cramps	5 (5%)	18 (3%)	0.61	1 (1%)	7 (1%)	1.00	8 (8%)	32 (6%)	1.00	0 (0%)	15 (3%)	0.14
- Musculoskeletal	1 (1%)	3 (1%)	1.00	0 (0%)	2 (<1%)	1.00	0 (0%)	16 (3%)	0.56	2 (2%)	4 (1%)	0.22
Fatigue	16 (16%)	59 (11%)	0.33	0 (0%)	10 (2%)	0.37	6 (6%)	23 (4%)	0.33	1 (1%)	4 (1%)	0.56
Neuropathy, any	12 (12%)	70 (13%)	0.46	1 (1%)	22 (4%)	0.23	9 (9%)	72 (13%)	0.76	5 (5%)	14 (3%)	0.19
- Motor	0 (0%)	14 (3%)	0.09	0 (0%)	4 (1%)	1.00	4 (4%)	16 (3%)	0.60	1 (1%)	6 (1%)	1.00
- Sensory	12 (12%)	66 (12%)	0.65	1 (1%)	21 (4%)	0.23	8 (8%)	68 (12%)	0.64	4 (4%)	12 (2%)	0.28
Hematological, any	16 (16%)	103 (18%)	0.23	21 (21%)	145 (26%)	0.38	6 (6%)	101 (18%)	<0.01	7 (7%)	42 (8%)	1.00
Lymphatics (edema)	1 (1%)	10 (2%)	0.70	0 (0%)	2 (<1%)	1.00	6 (6%)	25 (4%)	0.35	1 (1%)	5 (1%)	1.00
Hypertension	4 (4%)	27 (5%)	0.49	0 (0%)	9 (2%)	0.37	8 (8%)	56 (10%)	0.19	0 (0%)	3 (1%)	0.09

*The maximum grade per patient per adverse event is shown; *p-values show significance for grade 2-4 adverse events.*

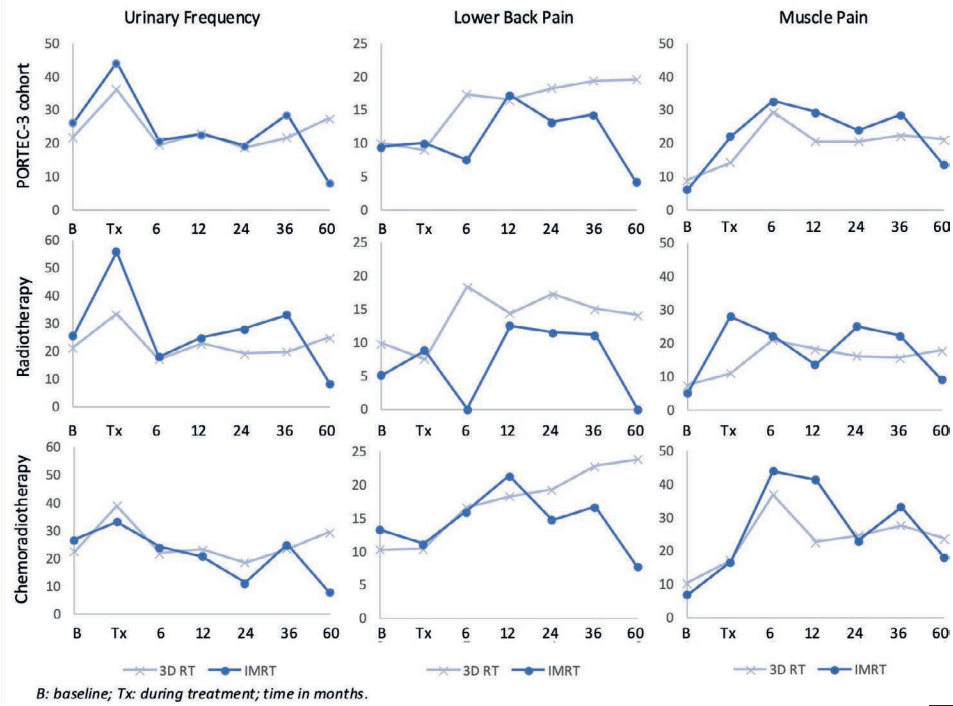
RT: radiotherapy; 3DCRT: 3D conformal radiotherapy.

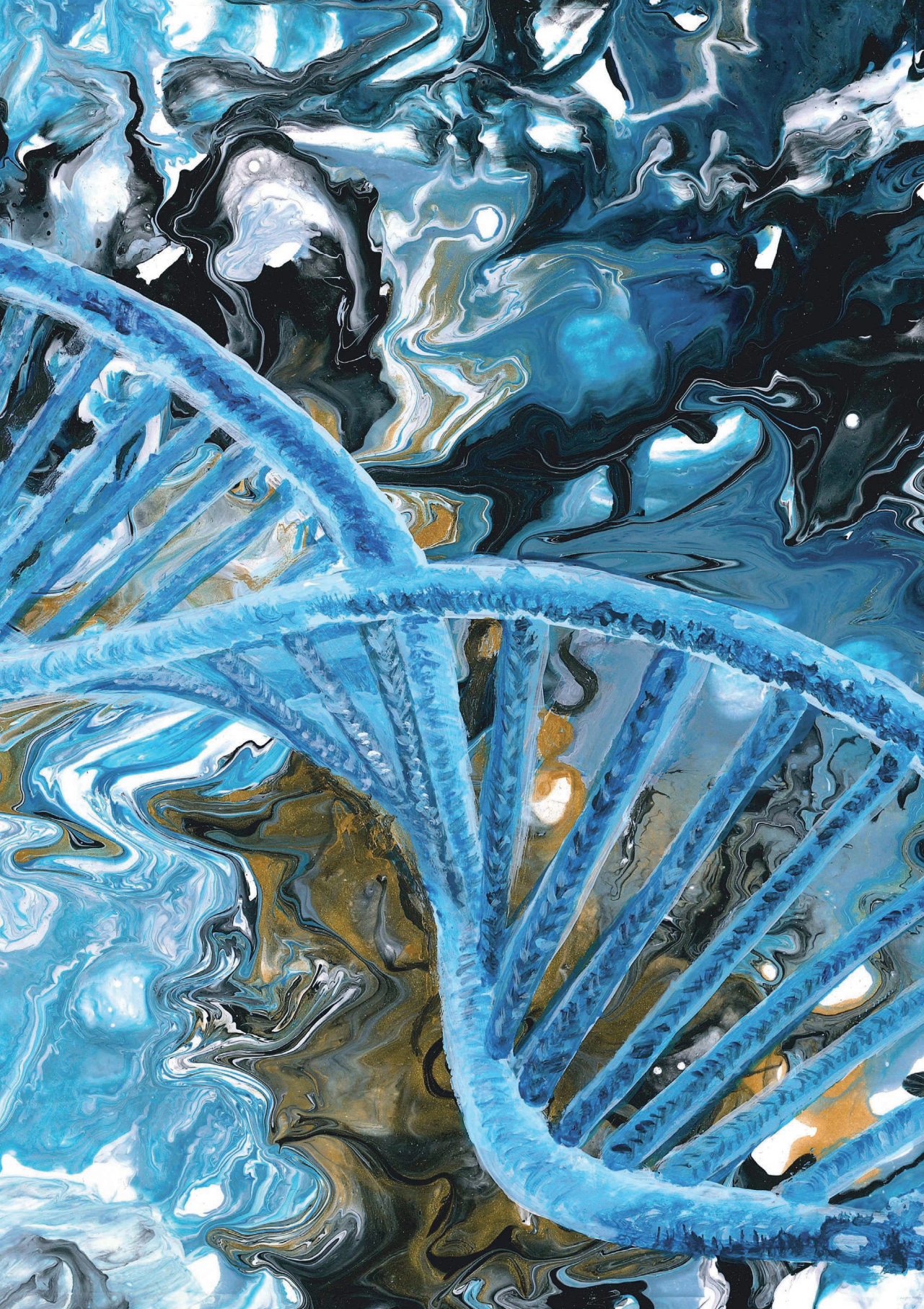
Figure E1. Dose distribution of 3D-conformal radiotherapy versus intensity-modulated radiotherapy.



***A.** Four field box technique; **B.** Seven field intensity modulated radiotherapy; **C.** Volumetric arc radiotherapy.*

Figure E2. Percentage of patients who reported "quite a bit" or "very much" of urinary frequency, lower back pain or muscle/joint pain in the total PORTEC-3 cohort, during and after radiotherapy only and after chemoradiotherapy.





CHAPTER 7

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

7. GENERAL DISCUSSION

The primary aim of this thesis was to evaluate the role of radiotherapy and to improve quality of treatment for women with endometrial cancer. The second aim of this thesis was to improve treatment selection and reduce over- and undertreatment by the integration of clinicopathological and molecular risk factors into the adjuvant treatment guidelines for women with endometrial cancer.

The guidelines for adjuvant treatment of women with endometrial cancer were largely based on results of the PORTEC, GOG and ASTEC/EN5 trials.[1-3] Conclusions from these trials were that external beam radiotherapy (EBRT) provides excellent locoregional control for women with early stage, intermediate and high-intermediate risk endometrial cancer, however, without a survival benefit and with added treatment-related toxicity, mostly gastro-intestinal symptoms. In the PORTEC-2 trial, vaginal brachytherapy was shown to be equally effective for local control and survival compared to EBRT, with reduced toxicity and better quality of life.[4-6] Long-term analysis of the PORTEC-2 trial showed persistent efficacy with a 10-year vaginal recurrence rate of 3.4% and overall survival of 69.5%, compared to 2.4% and 67.6% after EBRT, respectively, and the importance of new prognostic risk factors **(chapter 2)**. The pelvic recurrence rate was slightly higher after vaginal brachytherapy (6.3% versus 0.9% after EBRT), however these recurrences were mostly combined with distant metastasis, which highlights the need of improved understanding of tumour behaviour based on both clinicopathologic and molecular risk factors.

7.1 Risk factors in endometrial cancer

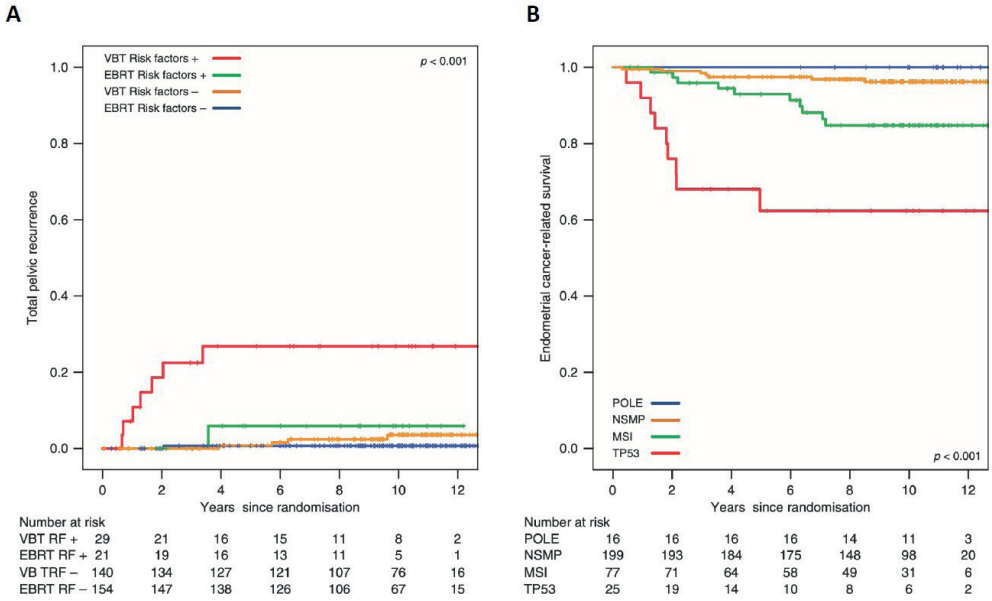
Well-known clinicopathological risk factors in endometrial cancer, associated with increased risk of disease recurrence, are age, histologic type and grade and FIGO stage. More recently discovered major risk factors such as (substantial) lymph-vascular space invasion (LVSI) and L1-cell adhesion molecule (L1CAM) overexpression, and molecular risk factors as defined by the Cancer Genome Atlas group (TCGA) and subsequently detected by surrogate markers in standard pathology specimens (*POLE*mut, NSMP, MMRd and p53abn), and ß-catenin (*CTNNB1*) exon 3 mutation are currently being implemented in the risk classification and treatment guidelines.[7-12] LVSI is associated with the risk of (microscopic) nodal and distant metastases and higher rates of recurrence, and reduced cancer-specific survival, both in the presence and absence of lymph node metastases.[13, 14] LVSI quantified as substantial, compared to no or focal LVSI, showed to be the strongest risk factor for pelvic and distant recurrences.[9, 15, 16] In *CTNNB1*-mutated endometrial cancer, the Wnt signalling pathway is activated by nuclear accumulation of ß-catenin that may result in endometrial cancer progression, and by abnormal expression of cell proliferation and progression genes.

CTNNB1 exon 3 mutation is associated with decreased overall survival.[17, 18] L1CAM is a membrane glycoprotein with an important role in tumour cell adhesion and migration. L1CAM overexpression (>10%) on immunohistochemistry is reported in approximately 16-28% of endometrial cancers and is associated with presence of *TP53* mutations, non-endometrioid histology, histological grade 3, and with LVSI. L1CAM overexpression was shown to be independently related with an increased risk of locoregional and distant spread, and decreased overall and relapse-free survival.[10-12, 19-21]

7.2 Combining clinicopathologic and molecular risk factors to guide adjuvant treatment

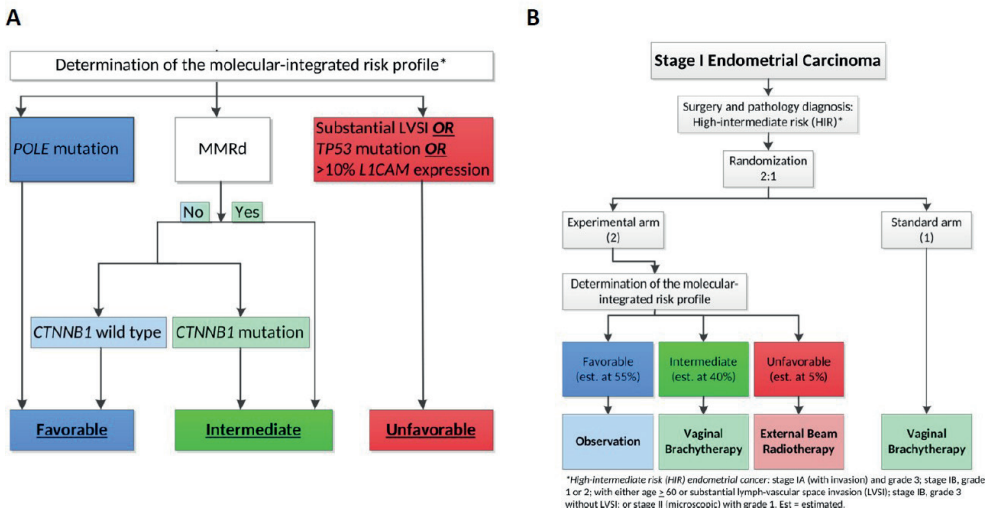
Analysis of the combination of clinicopathologic and molecular risk factors within the PORTEC-2 population showed that substantial LVSI, p53abn and L1CAM overexpression were all strongly associated with the risk of pelvic and distant recurrence and impaired endometrial cancer-related survival **(chapter 2)**. Patients with any of these risk factors who were treated with pelvic EBRT were found to have significantly improved pelvic control over those treated with vaginal brachytherapy (*Figure 1A*). These findings illustrate that within the (high-)intermediate risk group some women with risk factors as LVSI, L1CAM overexpression or p53abn may benefit from pelvic EBRT over VBT.

Figure 1. A) Total pelvic recurrence by unfavourable risk factors (substantial LVSI, p53abn or L1CAM overexpression). **B)** Endometrial cancer-related survival by 4 molecular subgroups.



In a combined analysis of the pooled PORTEC-1 and 2 trial cohorts of (high-)intermediate risk endometrial cancer treated with either EBRT, brachytherapy or observation, the TCGA subclasses and other molecular risk factors as *CTNNB1* mutation were combined with presence of substantial LVSI and L1CAM overexpression into an integrated molecular profile.[8, 9, 22] With the combination of all these risk factors, three subgroups of (high-)intermediate risk endometrial cancer with favourable, intermediate and relatively unfavourable outcomes could be defined. The favourable profile, comprising endometrial cancers with either *POLE* mutation or with absence of all the other risk factors had an excellent prognosis, with low risk of recurrence even without adjuvant treatment, and for this subgroup it was suggested that adjuvant treatment could safely be omitted (*Figure 1B*). For the small group with unfavourable profile with either p53abn, L1CAM overexpression or substantial LVSI, which was strongly associated with higher risk of locoregional and distant spread, adjuvant treatment by EBRT reduced pelvic recurrence as compared to vaginal brachytherapy. For those with an intermediate profile with either MMRd or *CTNNB1* exon 3 mutation, the most benefit of adjuvant vaginal brachytherapy is expected.[23] This molecular-integrated risk profile with corresponding consequences for adjuvant treatment is being investigated in the international, multicentre randomised PORTEC-4a trial for women with high-intermediate risk endometrial cancer (*Figure 2AB*).[24] In the PORTEC-4a trial women in the experimental arm receive adjuvant treatment based on their integrated molecular profile: those with a favourable profile receive no adjuvant treatment; those with an intermediate profile receive vaginal brachytherapy; and those with an unfavourable receive pelvic EBRT, while those in the control group all receive the standard adjuvant brachytherapy (*Figure 2B*).

Figure 2. A) Decision tree of the molecular-integrated risk profile. **B)** Study design of the PORTEC-4a trial.



The design of the PORTEC-4a trial showed a satisfactory patient acceptance rate of 35% even in the initiation phase of the trial, which ranged from 0 to 57% per institute **(chapter 3)**. Another challenge of the PORTEC-4a trial was the determination of the molecular profile within a narrow timeframe of 2 weeks, as patients had to start treatment within 6-8 weeks from surgery. The overall time between randomisation and determination of the molecular risk profile was 10.2 calendar days, and without the local LUMC cases for which no time was needed to send the tumour samples over, 12.2 days. In 15.6% of all cases pathology review lasted more than 2 weeks, mostly because of delayed receipt of the requested materials and the turnaround time of the NGS. Overall, this analysis showed that determining the molecular profile within time was a logistical challenge. Ideas to further optimise the logistical process may be a regional platform with digital image sharing, a joint laboratory information system and further implementation of molecular testing at regional hospitals.

The PORTEC-4a trial has recently completed accrual. In case the PORTEC-4a trial results will be positive, direct assessment of the molecular profile at the local cancer centre could greatly facilitate the logistical process. This can be achieved by using more widely available, faster and cheaper methods. MMR protein expression and p53 status assessed by immunohistochemistry showed high concordance and low interobserver variation, and first results of a faster and low-cost *POLE* test by PCR assays also showed high sensitivity and specificity.[25-27] Other pathology items that could be assessed at the local pathology lab are LVSI, quantified according to the three-tiered scoring system (no, focal or substantial LVSI), and L1CAM overexpression by immunohistochemistry. Determining the integrated molecular profile locally ensures timely decisions on adjuvant treatment for each individual patient.

7.3 Radiotherapy quality assurance

Within the PORTEC-4a trial an extensive quality assurance (QA) programme was performed to ensure uniform high-quality treatment, as institutes had limited experience with delineating on CT- or MRI-scans for single channel vaginal brachytherapy. Of 21 institutes participating in the dummy run of the PORTEC-4a trial, 15 (71.4%) needed minor or major adjustments of the vaginal brachytherapy plan **(chapter 4)**. Most common reasons for revisions were delineation of the CTV or OAR, dose planning and applicator reconstruction. With the revised brachytherapy plans, the range and standard deviation in dose parameters narrowed down to a more acceptable variation. Thereafter, during annual QA, still 5 out of 27 brachytherapy plans had major protocol deviations and in addition, several institutional changes were observed, such as change in treatment planning system, applicator set, type of afterloader and staff, all essential aspects of brachytherapy treatment. With these findings, QA in radiotherapy trials shows to be essential to

prevent trial protocol deviations and therewith possible impaired trial outcomes.[28, 29] Extensive QA increases treatment uniformity and ensures optimal treatment in the trial which leads to more reliable trial outcomes.[30-37] In a previous review on radiotherapy QA in randomised trials major protocol deviations were observed in 11.0–48.0% of cases, and were reported to be associated with impaired overall survival and local control and potentially increased treatment related toxicity.[28, 38] Besides the positive effect on treatment quality and uniformity within a trial, QA for vaginal brachytherapy will additionally result in increased reliability of data on dose parameters that can be used for evaluation of treatment effectiveness and brachytherapy related toxicity. For external beam radiotherapy, with the introduction of more conformal radiotherapy techniques as IMRT or VMAT, QA is of major importance, as delineation and treatment planning variations can result in significant alteration of dose distribution to the target volumes or OARs. In future radiotherapy trials, a comprehensive QA program, including a pre-trial dummy run and annual QA, should be strongly considered to be included in the trial design. Even though continuous QA within radiotherapy trials comes with additional costs and is labour-intensive to perform, the benefit of continuous QA seems to outweigh these disadvantages. Review of one case per institute per year could already increase protocol adherence, and therewith treatment quality and uniformity. In the near future, digital platforms for central review of radiotherapy data and the use of artificial intelligence for case-specific QA can facilitate fast QA procedures in future radiotherapy trials, for example by using statistical models to detect outliers of target volume delineation or dosimetry.[39-41]

7.4 Treatment-related toxicity and modern radiotherapy techniques

Vaginal brachytherapy is a treatment with very limited toxicity. Within the PORTEC-2 trial, of all women who received vaginal brachytherapy 5.6% reported quite a bit to very much diarrhoea after treatment, compared to 22.7% of those who received EBRT.[5] After vaginal brachytherapy lower scores of faecal leakage were reported six months after treatment, compared to EBRT. Both of these symptoms resulted in limitations of daily activities due to bowel problems for 6% of women after vaginal brachytherapy, versus 22% after EBRT.[42] Long-term analysis showed that, besides more bowel symptoms after EBRT, urinary urgency was significantly more frequent after EBRT compared to vaginal brachytherapy.[43] Symptoms of vaginal dryness, vaginal shortening/tightening or dyspareunia were not significantly different between vaginal brachytherapy or EBRT, even though a higher rate of grade 1 and 2 mucosal atrophy was observed from 6 months onwards after vaginal brachytherapy; 35% versus 17% at 3-years after vaginal brachytherapy versus EBRT, respectively. Toxicity of EBRT, however, has decreased over the past decade due to the implementation of new radiotherapy techniques. EBRT techniques have developed

from 3D-conformal radiotherapy towards more modern techniques as intensity-modulated radiotherapy techniques as IMRT or VMAT. Analysis of the EBRT techniques in the PORTEC-3 trial for high risk endometrial cancer showed that IMRT resulted in lower rates of grade $\geq$ 2 adverse events (67.7% versus 74.0%), which were mostly gastro-intestinal or haematological, and fewer patient-reported bowel symptoms, compared to 3D conformal radiotherapy **(chapter 5)**. Besides reducing the doses to the lower gastro-intestinal and genito-urinary tract, IMRT and VMAT can also better spare the bone marrow.[44-47] Previous studies showed that reduced radiation dose to the pelvic bone marrow resulted in significant fewer haematological adverse events, which in turn may result in improved clinical outcomes by increased tolerance for chemotherapy.[48-51] For future perspectives of EBRT, development and implementation of new modern radiotherapy techniques can result in fewer treatment-related toxicities and studies are ongoing. Exciting opportunities for the improvement of radiotherapy treatment can be expected from daily MR-guided adaptive radiotherapy, CT-based adaptation based on 4D cone-beam CT, and fast, automated treatment planning software. For vaginal brachytherapy, increased availability and use of CT or MRI can result in better visualisation of the target volume and organs-at-risk for each fraction. By using in-room CT, brachytherapy procedures could be performed more efficiently and patient-friendly.

All aforementioned developments can lead to decreased treatment margins, increased precision and decreased radiated volume of the organs-at-risk and therewith reduced treatment-related toxicity and patient-reported symptoms. Other radiotherapy modalities as proton beam radiotherapy are being introduced for gynaecological malignancies and may reduce dose to organs-at-risk even further, including bowel and bone marrow.[52-55] With these developments the future of radiation therapy beholds fewer toxicity and increased quality of life by more precise and image-guided adaptive therapy with improvement of clinical outcomes.

7.5 Pathology review

Pathology review by expert gynaecological pathologist in diagnosis and treatment of endometrial cancer is frequently performed, as previous studies have shown that pathology assessment of the female reproductive tract has the highest rates of discrepancies between the original and review pathology assessment.[56] Results of the pathology review of the PORTEC-1 and -2 trials showed that 14-24% of patients would not have been eligible for the trial based on the pathology review, mostly due to a shift in histological grade. This was also confirmed in a study of a large high grade endometrial cancer cohort.[57] **Chapter 6** describes the results of the upfront pathology review of the PORTEC-3 trial, before inclusion and randomisation. After reviewing 1226 pathology specimens, 102 patients (8.3%) were found not eligible and therefore not included in the trial. These findings show that without pathology review, 8% of patients could have been under or overtreated, and

could have received unnecessary toxic treatment. An additional benefit of upfront pathology review within clinical trials is that the trial population will consist of a truly eligible patients, which increases the reliability of the trial results.[56, 58, 59] Remaining challenges of routine pathology review by dedicated pathologists are the time-consuming aspect, the costs, and the logistical difficulties. These challenges can partly be solved by a reduction of inter-observer variation by subspecialisation of pathologists and increased use of fast digital pathology consults.

In the near future, significantly less inter-observer variation is expected when the molecular risk factors are implemented in the treatment guidelines which may lead to reduced need for pathology review. Only for rare (non-)endometrioid histologic subtypes with unusual molecular-histology combinations, pathology review should still be performed, especially in clinical trials.

7.6 Prognostic significance of molecular risk factors in endometrial cancer trial cohorts

The analysis of molecular risk factors within the PORTEC-2 trial population, as described in **chapter 2**, showed that out of 344 (high-)intermediate risk endometrial cancer samples 7.3% were p53abn, 4.7% *POLE*mut, 22.4% MMRd, 57.8% had no specific molecular profile and 2.9% were multiple classifiers. Similar analysis has been performed in the high risk population of the PORTEC-3 trial and showed quite a different distribution of the molecular subgroups. Of 423 high risk endometrial cancer samples 22.7% were p53abn, 12.4% *POLE*mut, 33.4% MMRd, 31.5% had no specific molecular profile and 7.1% were multiple classifiers. With this molecular subdivision, remarkable survival differences were observed. Patients with *POLE*mut endometrial cancer had excellent prognosis (98.0% recurrence-free and overall survival), while those with p53abn endometrial cancer had significantly worse prognosis (48.0% and 54.0% recurrence-free and overall survival).[60] Women with p53abn endometrial cancer had the largest benefit of the addition of chemotherapy with an absolute difference of 22.4% and 23.1% for recurrence-free and overall survival at 5 years, while for the MMRd subgroup no benefit of added chemotherapy was observed over EBRT alone. Within the NSMP subgroup the addition of chemotherapy showed a trend for improved recurrence-free survival, similar to the overall trial results; however, due to the limited number of NSMP endometrial cancer in this subanalysis, no definitive conclusions can be drawn for this group. The relatively small subgroup within the NSMP group with negative ER and PR receptors was recently shown to have worse prognosis and more often non-endometrioid histology.[61] Future challenges remain the further specification of risk characteristics within the NSMP group, and define optimal adjuvant treatment for each individual endometrial cancer patient based on the patient's specific risk factors.

7.7 Improving treatment selection by implementing molecular risk factors in the treatment guidelines

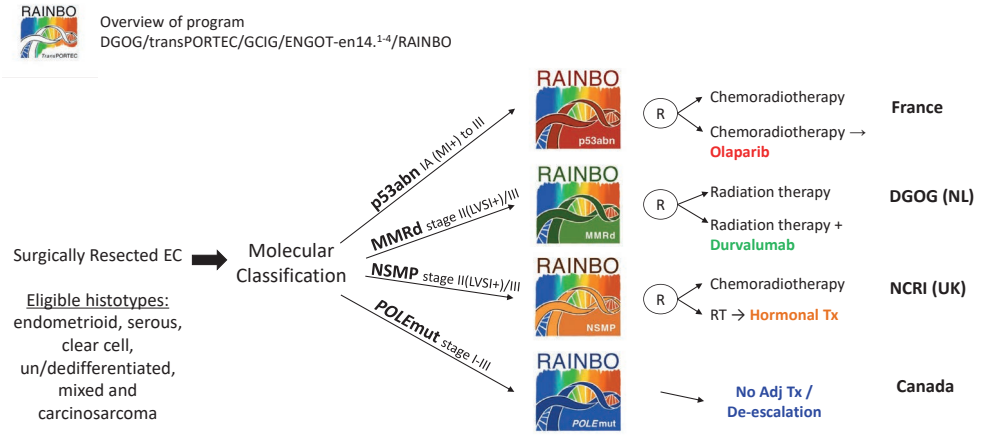
With the knowledge that has been gained on molecular risk factors in endometrial cancer, treatment selection can be improved by implementing these risk factors into the treatment guidelines. p53abn endometrial cancer, even when surgically staged as stage I, should be considered as high risk endometrial cancer and treated accordingly with EBRT and chemotherapy, as investigated by molecular analyses in the PORTEC-3 and in a Danish cohort.[60, 62] The PORTEC-3 trial showed 10% survival benefit for serous cancers of all stages with the addition of chemotherapy, serous cancers comprising about half of all p53abn endometrial cancers. What the exact benefit of added chemotherapy to EBRT will be for stage I (especially stage IA) p53abn endometrioid-type endometrial cancer remains to be investigated further.

Results of the PORTEC-4a trial may show the efficacy of EBRT alone on locoregional control rates and disease-free survival for early stage p53abn endometrioid endometrial cancer. In the GOG-249 trial, which included 20% of women with serous and clear cell cancers, pelvic EBRT had similar recurrence-free survival and better pelvic and para-aortic nodal control compared with the combination of vaginal brachytherapy and 3 cycles of chemotherapy.[63] Based on these findings, patients can be counselled in shared decision making about the survival benefit of adding chemotherapy to EBRT versus the extra treatment-related toxicity. Strikingly, for high risk MMRd endometrial cancers no benefit of chemoradiotherapy over EBRT alone was found in the molecular analysis of the PORTEC-3 trial, and adjuvant chemotherapy should not be recommended; ongoing trials are exploring checkpoint inhibition for MMRd cancers. For high risk (grade 3 and/or stage III) NSMP endometrial cancer a trend for improved recurrence-free survival was seen with chemoradiotherapy. For patients with stage I-II EC with substantial LVSI or L1CAM overexpression EBRT should be recommended, as there is an increased risk of locoregional spread of the disease and EBRT showed excellent locoregional control for this subgroup in the PORTEC-2 cohort (**chapter 2**). *POLE*mut endometrial cancer is associated with excellent prognosis, even in the series which are available without adjuvant treatment, and omission or de-escalation of adjuvant treatment should therefore be considered especially for stage I and II *POLE*mut endometrial cancer. For the very rare stage III *POLE*mut cancers more evidence is needed. These findings and treatment principles are the subject of new and ongoing trials, and treatment recommendations based on molecular integrated risk groups have recently been implemented in the updated European guidelines for endometrial cancer of the European Society of Gynaecological Oncology, Radiation Oncology and Pathology (ESGO-ESTRO-ESP) Guidelines Committee (*Table 1*).[64, 65]

7.8 Future targets for treatment related to the molecular classification

The characteristics of the four molecular groups have led to new possibilities for targeted treatments and/or altered treatment strategies. A new research program for women with high risk EC, with a specific trial for each of the four molecular subgroups is the RAINBO study program, which is a collaboration between large international research groups and is based on the molecular classification and translational research within the *Trans*PORTEC research consortium. The RAINBO platform consists of four different studies targeting each different molecular subgroup, with overarching aims of evaluating the impact on survival and quality of life with targeted treatments, and with an overarching biobank for further translational research (*Figure 3*).[66]

Figure 3. RAINBO study program.



RAINBO program supported by GCIG and coordinated by *Trans*PORTEC will allocate EC pts to 4 international academic sub-trials each led by one Gyn-Onc national clinical trial group

Table 1. Risk groups in endometrial cancer according to PORTEC and the ESMO-ESGO-ESTRO guideline, including the molecular-integrated risk groups.

Risk Group	PORTEC (2002-2013)[1]	ESMO-ESGO-ESTRO guideline 2021[65]	ESMO-ESGO-ESTRO guideline 2021 Molecular-integrated risk groups[65]
Low	FIGO stage IA EEC: grade 1-2	FIGO stage IA EEC: grade 1-2, LVSI neg.	FIGO stage I-II EEC: *POLE*mut
			FIGO stage IA EEC: MMRd/NSMP, grade 1-2, no or focal LVSI
Intermediate	FIGO stage IB EEC: grade 1-2, age <60	FIGO stage IB EEC: grade 1-2, LVSI neg.	FIGO stage IA EEC: MMRd/NSMP, grade 3, no or focal LVSI
		FIGO stage IA EEC: grade 3, LVSI neg.	FIGO stage IA NEEC or p53abn EEC: without myometrial invasion
		FIGO stage IA NEEC: no myometrial invasion	FIGO stage IB EEC: MMRd/NSMP, grade 1-2, no or focal LVSI
High-intermediate	FIGO stage IA EEC: grade 3, age ≥60	FIGO stage IA/B EEC: grade 1-3, LVSI pos.	FIGO stage I EEC: MMRd/NSMP, substantial LVSI
	FIGO stage IB EEC: grade 1-2, age ≥60	FIGO stage IB EEC: grade 3, LVSI neg.	FIGO stage IB EEC: MMRd/NSMP, grade 3
		FIGO stage II EEC	FIGO stage II EEC: MMRd/NSMP
High	FIGO stage IB EEC: grade 3	FIGO stage III-IVA EEC without residual disease	FIGO stage III-IVA EEC: MMRd/NSMP
	FIGO stage II-III EEC	FIGO stage I-IVA NEEC: without residual disease	FIGO stage I-IVA EEC: p53abn with myometrial invasion
	FIGO stage I-III NEEC		FIGO stage I-IVA NEEC: MMRd/NSMP with myometrial invasion

EEC endometrioid endometrial cancer; LVSI lymph-vascular space invasion (neg.: negative, pos.: substantial LVSI); NEEC non-endometrioid endometrial cancer (serous or clear cell carcinoma);

7.8.1 Adjuvant treatment for p53abn endometrial cancer

p53abn endometrial carcinomas are associated with unfavourable prognosis and higher stage of disease; 7.3% of the PORTEC-2 (high-)intermediate risk samples were p53abn versus 22.7% of the high risk endometrial cancer samples of the PORTEC-3. This subgroup has the largest benefit of the addition of chemotherapy (22.4% and 23.1% for RFS and OS).[60] Both amplification of the human epidermal growth factor receptor 2 (Her-2/Neu) and homologous recombination deficiency (HRd) are frequent molecular alterations in p53abn endometrial cancer. Within the PORTEC-3 translational research, 25% of p53abn endometrial cancers were found HER2 positive.[67] The HER-2/Neu receptor is a potential target for therapy, however, studies using HER-2/Neu inhibitors as monotherapy have had disappointing results.[68-71] In a recent study, the combination of trastuzumab with carboplatin and paclitaxel chemotherapy in HER-2/Neu-positive serous carcinomas resulted in a prolonged median progression-free survival in the carboplatin-paclitaxel alone group (13 vs. 8 months, p=0.005), with the largest benefit for stage III-IV disease (17.7 vs. 9.3 months, p=0.005).[72, 73] Homologous recombination is essential for repair of DNA double-strand breaks, which is mediated by (among others) BRCA1 and BRCA2 proteins, and deficiency (HRd) is reported in 46% of p53abn endometrial cancer. Targeting HRd in endometrial cancer by using platinum-based chemotherapy and/or PARP inhibitors seem promising therapeutic options.[74] PARP, or poly (ADP-ribose) polymerase, is involved in DNA damage detection and generation of poly (ADP ribose) chains. These chains facilitate chromatin remodelling and DNA repair. Loss of PARP results in persistent single strand DNA breaks and eventually in double-strand DNA breaks (DSBs). Normally, DSBs are repaired by homologous recombination or other repair mechanisms such as non-homologous end joining. Tumour cells with either loss of PARP or with HRd are still viable, although more faulty DNA repair occurs. However, in case of simultaneous inhibition of both factors, accumulation of DSBs leads to cell death.[75, 76] Response rates of 31-40% to PARP inhibitors (PARPi) have been reported in HRd ovarian carcinoma and BRCA-mutated breast cancer.[77, 78] Within the p53abn-Red trial of the RAINBO program, women with p53abn endometrial cancer will be randomised to chemoradiotherapy versus chemoradiotherapy with the PARP inhibitor olaparib.

7.8.2 Adjuvant treatment of MMR deficient endometrial cancer

The MMRd subgroup comprises 30% of all endometrial cancers and has an intermediate prognosis.[7, 8, 79-82] MMRd endometrial cancers fail to express one or more of the MMR proteins, leading to the accumulation of mismatches, deletions, and microsatellite instability. The majority (~ 75%) of MMRd endometrial cancers are MMR deficient due to MLH-1 promoter hypermethylation with subsequent loss of MLH1 protein expression, and another 10-15% are due to biallelic somatic mutations or other DNA defects.[83] The remaining 10% are caused by germline defects in one of the

MMR genes (Lynch syndrome). Within the entire endometrial cancer population, the frequency of Lynch syndrome varies between 3-6%.[83, 84] MMRd endometrial cancers are hypermutated tumours that harbour higher neoantigen loads, which are associated with increased immune response by cytotoxic CD8+ tumour-infiltrating lymphocytes (TILs).[80-82, 85-93] The presence of CD8+ TILs has been investigated within the PORTEC-1 and 2 cohort and showed that the TIL density was a strong predictor of disease recurrence.[94] MMRd tumours have an increase of PD-1 and PD-L1 expression, which makes these tumours attractive for immune checkpoint inhibitors.

Previous trials have confirmed this hypothesis and have shown response rates of 13-48% to checkpoint inhibitors such as nivolumab, pembrolizumab and dostarlimab in women with recurrent or metastatic hypermutated tumours, including endometrial cancer.[95-98] The addition of the PD-L1 inhibitor durvalumab to the radiotherapy will be investigated in the MMRd-Green trial of the RAINBO program.

7.8.3 Adjuvant treatment of endometrial cancer with no specific molecular profile (NSMP)

The subgroup with no specific molecular profile is a heterogeneous group of tumours with a low mutational burden, and mostly comprises endometrioid-type cancers of low to intermediate grade. Within this subclass about 85-90% of cancers are hormone receptor positive. Hormone receptor status was found to be an important prognostic factor, and loss of ER or PR expression is related to higher grade tumours, non-endometrioid histology, L1CAM overexpression, substantial LVSI and impaired disease-free survival.[61, 99-101] A recent analysis showed that only among the NSMP group, histological grade is still a significant prognostic factor.[102] Analysis of the PORTEC-3 NSMP subgroup showed that the large majority of tumours were ER and PR positive. Targeting the endocrine receptors by hormonal therapy is currently only used for women that wish the preserve fertility with low grade early-stage disease, and in those with advanced or metastatic low grade disease. As hormonal therapy for women with low grade ER+/PR+ NSMP tumours might effectively reduce relapse with a better toxicity profile than chemotherapy, the addition of hormonal therapy to radiotherapy will be compared with chemoradiotherapy in the NSMP-Orange trial of the RAINBO program.

7.8.4 De-escalation of adjuvant therapy for POLE-mutant endometrial cancer

POLE mutations are more frequently found in relatively younger women with lower BMI and higher grade endometrioid endometrial tumours compared to *POLE* wildtype EC.[7, 8, 79, 103-108] In *POLE*mut endometrial cancers, which are ultramutated cancers, increased antitumour response by peritumoral and tumour-infiltrating CD8+ lymphocytes has been reported, most

probably because the mutated DNA fragments act as neo-antigens that elicit a strong immune response.[88-90, 109, 110] In contrast to the poorly differentiated microscopic appearance of *POLE*mut endometrial cancers, they have consistently been shown to have an excellent prognosis with only an occasional relapse, both with and without adjuvant treatment.[62] It has been suggested that their very favourable outcome is mainly based on their ultramutated phenotype with many mutated DNA fragments, which elicit a strong host immune response.[88] In addition, these ultramutated cells might not be able to function properly and DNA replications and consequently cell division and potential for spread may be impaired. De-escalation or omission of adjuvant treatment could be considered in *POLE*mut endometrial cancers, and this will be prospectively investigated in the POLE-Blue trial of the RAINBO program.[8, 79, 91, 103, 105-107, 111]

8. CONCLUSION

Vaginal brachytherapy has been shown to be the current best adjuvant treatment for women with early stage, (high-)intermediate risk endometrial cancer, balancing maximal local control with lowest toxicity. The risk of recurrence is strongly associated with risk factors as substantial LVSI, L1CAM overexpression and p53abn. Women with these risk factors should be treated with adjuvant external beam radiotherapy instead of vaginal brachytherapy to maximise pelvic control and recurrence-free survival. Using a molecular-integrated risk profile to determine adjuvant treatment in early stage, high-intermediate risk disease might optimize outcomes and spare many women adjuvant treatment. This rationale is currently being investigated in both the PORTEC-4a and TAPER trials, and in the coming years the results will show if molecular risk factors should be used to determine adjuvant treatment.[24, 112] Molecular alterations are frequently found in endometrial cancer and increasing knowledge on their prognostic significance and possible therapeutic options has been gained. Trials investigating (adjuvant) treatment based on molecular alterations for women with (high-)intermediate risk, high risk and recurrent or metastatic endometrial cancer are ongoing. New treatment targets have emerged and are being investigated in trials for localised, advanced and metastatic disease. Moreover, radiotherapy techniques for endometrial cancer have been improving over time. Modern radiotherapy techniques have the ability to increasingly spare the surrounding healthy tissues with similar or improved oncological outcomes and fewer treatment related toxicities. Future developments can be expected in daily image-guided adaptive radiotherapy and improved use of innovative modalities which reduce the dose to the organs-at-risk. Future radiotherapy trials should incorporate adequate quality assurance programs, including dummy run and annual quality assurance, to achieve uniform high-quality treatment. All of these developments will lead to better outcomes and highest quality of life for women with endometrial cancer.

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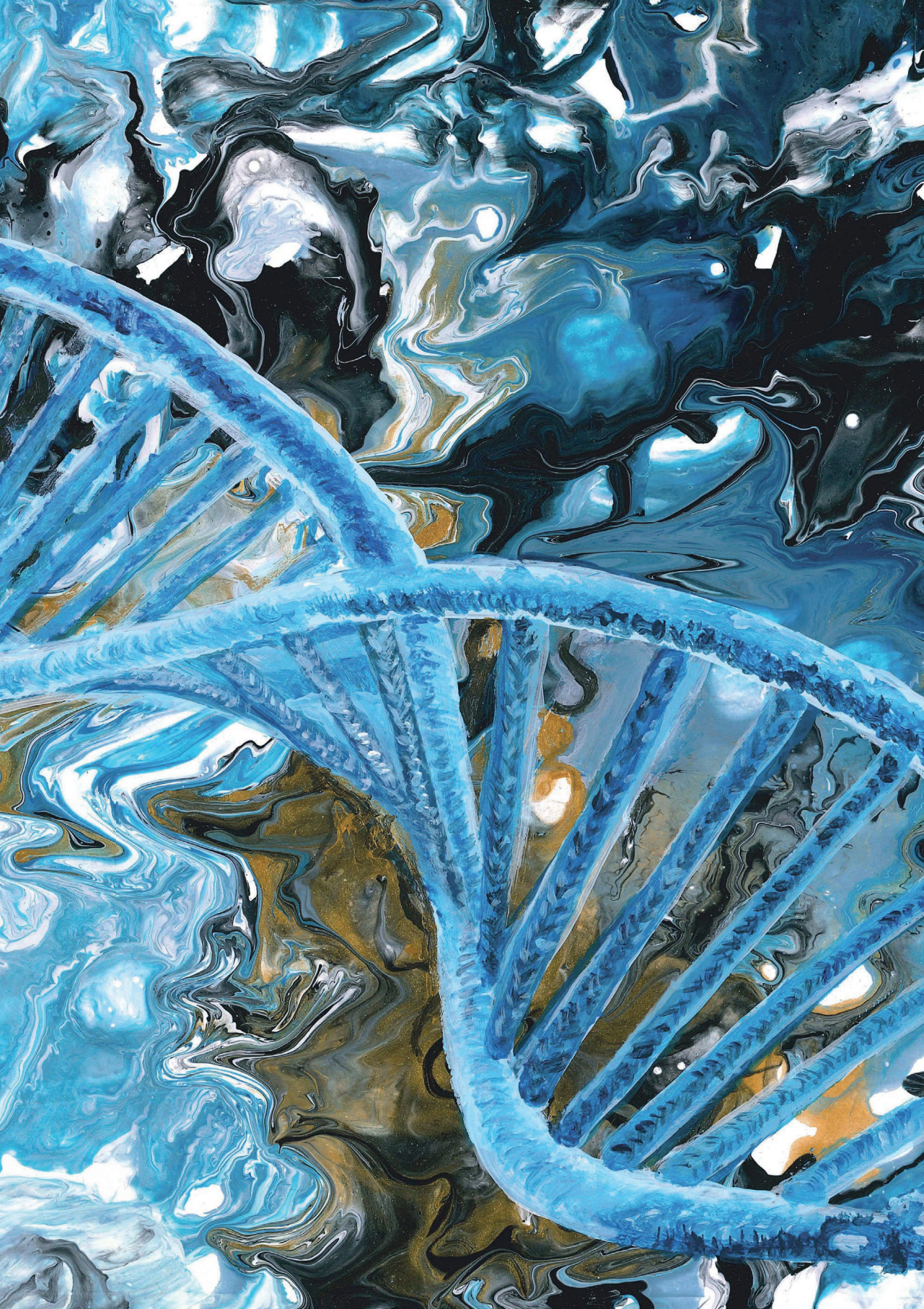
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APPENDICES

NEDERLANDSE SAMENVATTING
LIST OF PUBLICATIONS
DANKWOORD
CURRICULUM VITAE

NEDERLANDSE SAMENVATTING

Introductie

Het endometriumcarcinoom (baarmoederkanker) is de meest voorkomende gynaecologische kanker in ontwikkelde landen, met de hoogste incidentie bij postmenopauzale vrouwen tussen 65 en 85 jaar. De incidentie is de afgelopen jaren gestegen als gevolg van de toegenomen prevalentie van diabetes en obesitas en de vergrijzing van de bevolking. De diagnose wordt grotendeels in een vroeg stadium van de ziekte gesteld, vanwege vroege symptomen zoals vaginaal bloedverlies. Dit resulteert over het algemeen in een gunstige prognose en een relatief lage kankergerelateerde sterfte. Het meest voorkomende (ongeveer 70-80%) histologische type is het endometrioïd adenocarcinoom. Daarnaast is ongeveer 5-10% een sereus type en 1-5% een heldercellig type endometriumcarcinoom. Andere agressievere subtypen zijn het ongedifferentieerde endometriumcarcinoom en het carcinosarcoom.

De standaardbehandeling van het endometriumcarcinoom is een operatie, bestaande uit laparoscopische of abdominale hysterectomie en bilaterale salpingo-ovariëctomie (verwijdering van de baarmoeder en eierstokken), met in sommige gevallen lymfeklierdissectie of schildwachtklieroperatie. De indicatie voor aanvullende adjuvante behandeling hangt af van klinisch-pathologische risicofactoren, zoals leeftijd, histologisch type en graad, International Federation of Gynecology and Obstetrics (FIGO)-stadium, diepte van myometriuminvasie en aanwezigheid van lymfekliermetastasen en lymfebaan invasie (LVSI). Op basis van deze risicofactoren zijn vier risicogroepen (met laag, intermediair, hoog-intermediair en hoog risico) gedefinieerd, waarbij elke risicogroep een andere prognose heeft, en specifieke adviezen voor adjuvante behandeling

Laag risico endometriumcarcinoom

Vrouwen met een laag risico endometriumcarcinoom hebben na de operatie een zeer lage kans op een recidief, ook zonder adjuvante behandeling (5-jaars ziekte vrije overleving van meer dan 95%). Daarom wordt voor deze groep patiënten geen adjuvante behandeling geadviseerd.

Intermediair en hoog-intermediair risico endometriumcarcinoom

In Nederland is vaginale brachytherapie de huidige standaard adjuvante behandeling voor intermediair en hoog-intermediair risico endometriumcarcinoom, met uitzondering van patiënten met een intermediair risico endometriumcarcinoom die jonger dan 60 jaar zijn. Deze behandeling is gebaseerd op de uitkomsten van de PORTEC-1 en 2 studies. In de PORTEC-1 studie werden vrouwen met een vroeg stadium endometriumcarcinoom gerandomiseerd tussen uitwendige bestraling van

het bekken en geen adjuvante radiotherapie. Uitkomsten toonden significant minder locoregionale recidieven in de arm met uitwendige radiotherapie, maar geen verschil in overleving tussen beide armen. Met name vrouwen met een hoog-intermediair risico endometriumcarcinoom hadden het meeste voordeel van uitwendige radiotherapie. In de daarop volgende PORTEC-2 studie werd vaginale brachytherapie met uitwendige radiotherapie van het bekkengebied vergeleken met voor vrouwen met een hoog-intermediair risico endometriumcarcinoom. In totaal werden 427 vrouwen gerandomiseerd tussen 2002 en 2006. Hoofdstuk 2 beschrijft de lange termijn uitkomsten van deze studie. Na 10 jaar was het lokaal recidief percentage gelijk voor de groep met brachytherapie en die met uitwendige radiotherapie en was er geen verschil in overleving. Wel waren er minder door de patiënten gerapporteerde bijwerkingen na brachytherapie in vergelijking met uitwendige radiotherapie. Op basis van deze gegevens moet vaginale brachytherapie standaard worden geadviseerd voor vrouwen met een hoog-intermediair risico endometriumcarcinoom.

In de PORTEC-2 studie was het aantal recidieven in het bekkengebied hoger na vaginale brachytherapie (6,3% versus 0,9% bij uitwendige radiotherapie), echter werden deze recidieven meestal tegelijkertijd met metastasen op afstand gediagnosticeerd. Dit benadrukt de noodzaak van meer onderzoek naar het tumorgedrag op basis van zowel klinisch-pathologische als moleculaire risicofactoren. Evaluatie van gecombineerde klinisch-pathologische en moleculaire risicofactoren in de PORTEC-2 populatie toonden aan dat L1CAM overexpressie (>10%), *TP53*-mutatie en substantiële LVSI belangrijke risicofactoren waren voor het krijgen van een recidief in het bekkengebied of uitzaaiingen op afstand. In deze analyse bleek uitwendige radiotherapie een betere locoregionale controle te geven dan vaginale brachytherapie. Voor deze kleine groep lijkt uitwendige radiotherapie van het bekken de voorkeur te hebben om de locoregionale controle te maximaliseren.

Hoog risico endometriumcarcinoom

Vrouwen met een hoog risico endometriumcarcinoom hebben een hoger risico op metastasen, zowel lymfkliermetastasen in het bekkengebied als metastasen op afstand, en meer kankergerelateerde sterfte. In de huidige behandelrichtlijnen wordt voor deze vrouwen uitwendige radiotherapie van het bekken geadviseerd, met of zonder adjuvante chemotherapie. De rol van adjuvante chemotherapie in combinatie met uitwendige radiotherapie is onderzocht in verschillende gerandomiseerde studies. De PORTEC-3-studie onderzocht adjuvante radiotherapie alleen versus radiotherapie in combinatie met chemotherapie voor vrouwen met een hoog risico endometriumcarcinoom. De resultaten toonden een verbeterde recidiefvrije en algehele overleving na gecombineerde radiotherapie en chemotherapie in vergelijking met alleen radiotherapie, echter met meer behandelingsgerelateerde toxiciteit. Radiotherapie in combinatie met chemotherapie wordt vooral aanbevolen voor vrouwen met stadium III-ziekte en met sereus type endometriumcarcinoom. Chemotherapie alleen zou kunnen worden overwogen

voor vrouwen met meer uitgebreid stadium III-IV endometriumcarcinoom, echter werden in de gerandomiseerde GOG-258 studie vaker recidieven in het bekken- en para-aortaal gevonden dan met gecombineerde radiotherapie en chemotherapie.

Adjuvante behandeling op basis van een moleculair risicoprofiel

In 2013 analyseerde de Cancer Genome Atlas Group (TCGA) de moleculair genetische basis van de ontwikkeling van endometriumcarcinoom, die cruciaal is geweest voor het begrijpen van de moleculaire routes die betrokken zijn bij de ontwikkeling van het endometriumcarcinoom. De TCGA onderscheidde 4 verschillende moleculaire groepen. De groep met de meest gunstige prognose was de 'ultra gemuteerde' groep, welke wordt gekenmerkt door mutaties in het exonuclease domein van DNA-polymerase-epsilon (*POLE*). Daarnaast zijn er twee groepen met een intermediaire prognose, namelijk de hypergemuteerde groep, gekenmerkt door microsatelliet-instabiliteit (MSI) en mismatch repair deficiëntie (MMRd), en de groep gekenmerkt door laag aantal copy number afwijkingen zonder specifiek moleculair profiel (NSMP). De groep met meest ongunstige prognose wordt gekenmerkt door *TP53*-mutaties (p53abn of serous-like genoemd), met als histologisch type non-endometrioïde tumoren, voornamelijk het sereus type endometriumcarcinoom. Verschillende onderzoeksgroepen hebben de vier TCGA-subklassen onderzocht en gevalideerd in verschillende endometriumcarcinoom-cohorten. De implementatie van deze vier moleculaire groepen in de adjuvante behandeling voor vrouwen met hoog-intermediair risico endometriumcarcinoom wordt momenteel onderzocht in de gerandomiseerde PORTEC-4a-studie, met als doel meer gepersonaliseerde behandeling te geven en over- en onderbehandeling te voorkomen. In deze studie worden vrouwen 1:2 gerandomiseerd tussen de standaard behandeling (vaginale brachytherapie) en een experimentele arm waarin op basis van een geïntegreerd moleculair profiel wordt bepaald of, en welke adjuvante behandeling de patiënten krijgen. Bij een gunstig moleculair profiel (*POLE*-mutatie of geen van de andere kenmerken) wordt geen adjuvante behandeling gegeven, gezien de gunstige prognose. Bij een intermediair moleculair profiel (MMRd of NSMP met beta-catenine exon3 mutatie) wordt de standaard behandeling vaginale brachytherapie gegeven, en bij een ongunstig risicoprofiel (substantiële LVSI, L1CAM overexpressie, of p53abn) wordt uitwendige radiotherapie van het bekkengebied geadviseerd. De studie heeft inmiddels volledige instroom bereikt en de resultaten worden eind 2024 verwacht.

Patiëntacceptatie en logistieke haalbaarheid van de PORTEC-4a studie

Onderdeel van de PORTEC-4a studie was een evaluatie van de pilotfase na inclusie van de eerste 50 patiënten. Tijdens deze evaluatie werd de patiëntacceptatie, maar ook de logistieke haalbaarheid onderzocht, aangezien patiënten binnen het krappe tijdbestek van 8 weken na chirurgie moesten

starten met de adjuvante behandeling. De resultaten van deze evaluatie worden beschreven in hoofdstuk 3. In totaal waren in deze pilotfase 145 patiënten geïnformeerd over de studie, waarvan 50 (35%) uiteindelijk informed consent hebben gegeven. De meest voorkomende redenen om niet deel te nemen aan de studie waren: niet willen deelnemen aan een studie in het algemeen, en niet willen riskeren om geen behandeling te krijgen in de experimentele arm. Analyse van de logistieke haalbaarheid toonde een gemiddelde duur van 5.8 dagen van opvragen tot ontvangst van het PA-materiaal, en resultaat van het moleculair profiel in gemiddeld 10.2 dagen na ontvangst van het materiaal (range 1-23 dagen na randomisatie). 84% van de moleculaire profielen kon binnen de gestelde tijd van 2 werkweken worden bepaald. Met deze resultaten bleek de PORTEC-4a een goed lopende studie te zijn met een uitstekende patiëntacceptatie en logistieke workflow. Mogelijkheden om in de toekomst de logistieke workflow nog verder verbeteren zijn een regionaal platform met digitale beeldуitwisseling, gezamenlijk informatiesystemen en verdere implementatie van (goedkopere) moleculaire testen in de regionale ziekenhuizen.

Quality assurance in radiotherapie studies

In de PORTEC-4a studie wordt ongeveer 60% van de vrouwen behandeld met vaginale brachytherapie. Echter hadden de deelnemende instituten, tijdens de start van de PORTEC-4a studie in 2016, beperkte ervaring met het gebruik van CT of MRI bij single channel vaginale brachytherapie. Om de kwaliteit van de brachytherapie te evalueren was een quality assurance (QA) programma, bestaande uit een dummy run en jaarlijkse QA, onderdeel van de studie. De evaluatie van de dummy run en QA wordt beschreven in hoofdstuk 4. Tijdens de eerste dummy run voldeed 71,4% van de deelnemende instituten niet aan het studie protocol en werd feedback gegeven waarna het plan werd aangepast. Tussen de eerste en de tweede inzending verbeterde het plan en daalde de gemiddelde dosis in de vaginatop (gemiddelde van de twee referentiepunten A1 en A3 op 5mm van de cilinder) van 100,7% naar 99,9% en de spreiding van de gemiddelde dosis per instituut van 83,6-135,1 naar 96,4-101,4. Tijdens de jaarlijkse QA rondes voldeed de overgrote meerderheid (81.5%) van de brachytherapie plannen aan de vereisten van het studieprotocol. Echter werden er in 18.5% van de ingestuurde plannen grotere afwijkingen van het studieprotocol gevonden, meestal gerelateerd aan de intekening van het doelvolume of de risico-organen, de gemiddelde dosis in de vaginatop of de referentie volume lengte. Deze evaluatie laat zien dat een succesvolle initiële dummy run geen garantie is voor uniforme en hoge kwaliteit van de brachytherapie planning tijdens de looptijd van de studie, en dat jaarlijkse controle van tenminste 1 plan per instituut noodzakelijk is in toekomstige radiotherapie studies. Hoewel continue QA extra kosten met zich meebrengt en arbeidsintensief is, lijkt het voordeel van continue QA op te wegen tegen deze nadelen. In de nabije toekomst kunnen digitale platformen voor centrale beoordeling en snelle uitwisseling van radiotherapiegegevens bijdragen aan een

vergemakkelijking van dit proces. Ook het gebruik van kunstmatige intelligentie voor casus-specifieke QA kan de QA-procedure in toekomst vergemakkelijken, door bijvoorbeeld statistische modellen te gebruiken om uitschieters van intekeningen of dosimetrie te detecteren.

(Upfront) PA revisie bij het endometriumcarcinoom

De pathologie van gynaecologische tumoren heeft de grootste variatie in beoordelingen tussen verschillende pathologen. Onderzoek binnen de PORTEC-1 en 2 studies liet zien dat 24% respectievelijk 14% van de geïncludeerde patiënten achteraf gezien na revisie van de pathologie door een gespecialiseerde gynaeco-patholoog niet in aanmerking kwamen voor deelname aan de studie. De meest voorkomende discrepantie was beoordeling van de histologische graad, vooral de intermediaire graad (graad 2). In een andere studie naar hooggradig endometriumcarcinoom was ook de histologische subtypering een veelvoorkomende discrepantie. In de PORTEC-3 studie werd voorafgaand aan deelname PA revisie door een gespecialiseerde patholoog uitgevoerd om te verifiëren of patiënten daadwerkelijk in aanmerking kwamen voor deelname, en dus geen onnodige toxische behandeling zouden krijgen. De resultaten hiervan staan beschreven in hoofdstuk 5. Van de 1226 pathologie verslagen veranderde bij 43% 1 of meerdere items in het verslag, 8% veranderde daardoor dusdanig dat deze patiënten niet meer in aanmerking kwamen voor deelname aan de studie. Meest frequent werd dit veroorzaakt door verandering van het histologische subtype, de histologische graad of de endocervicale stromale betrokkenheid.

Standaard pathologie revisie is essentieel om de inclusie van de beoogde onderzoekspopulatie te verzekeren en om onder- of overbehandeling te voorkomen, vooral wanneer het gaat om behandelingen met substantiële toxiciteit. Uitdagingen van standaard revisie zijn echter het tijdrovende aspect, de kosten en de complexe logistieke workflow. Echter, in de nabije toekomst zal minder variatie worden verwacht tussen de beoordelingen van pathologen wanneer de moleculaire risicofactoren worden geïmplementeerd in de behandelrichtlijnen. Met deze objectievere risicofactoren zullen er minder discrepanties zijn en zal de noodzaak van standaard PA revisie verminderen. Ook de ontwikkeling om laaggradig versus hooggradig te onderscheiden, vooral bij NSMP tumoren, zal aan uniformiteit bijdragen. Alleen voor (niet-)endometrioïd type met ongebruikelijke moleculair-histologische combinaties, moet PA revisie nog steeds worden overwogen, met name in studieverband.

Verbetering van radiotherapie technieken

In de afgelopen 10 tot 20 jaar hebben de radiotherapietechnieken zich ontwikkeld van 2-dimensionaal geplande radiotherapie tot drie- en vierveldtechnieken en 3D-conformele radiotherapie (3DCRT). De meest recente ontwikkelingen zijn 3D-beeldgestuurde intensiteits-

gemoduleerde radiotherapie (IMRT) en volumetric-modulated arc therapy (VMAT). Met de introductie van meer geavanceerde radiotherapietechnieken waarbij de hoge dosis met smalle marge rond het doelgebied wordt gepland en de omringende organen beter worden gespaard, wordt verwacht dat behandelingsgerelateerde toxiciteit kan worden verminderd. In de PORTEC-3 studie werd 85% van de vrouwen behandeld met 3DCRT en ongeveer 15% met de modernere IMRT techniek. In hoofdstuk 6 wordt het effect van beide technieken op toxiciteit en kwaliteit van leven in de PORTEC-3 studie beschreven. Tijdens de behandeling werden geen significante verschillen waargenomen in door de arts gerapporteerde toxiciteit tussen beide technieken, behoudens een trend voor meer graad ≥3 toxiciteit na 3DCRT, voornamelijk hematologische en gastro-intestinale toxiciteit. Tijdens de follow-up werden hematologische en gastro-intestinale toxiciteit significant vaker gerapporteerd na 3DCRT in vergelijking met IMRT. Door de patiënten gerapporteerde symptomen (geen of 'een beetje', versus 'nogal' of 'heel erg') toonden geen significante verschillen tussen beide technieken, maar wel een trend voor minder darmklachten, zoals drang, krampen en diarree, na IMRT. In andere studies werden vergelijkbare afname van toxiciteit na IMRT vergeleken met 3DCRT. Daarom moeten intensiteits-gemoduleerde technieken zoals IMRT of VMAT de standaardtechnieken zijn voor de adjuvante behandeling van vrouwen met een endometrium carcinoom.

Dat IMRT en VMAT kunnen leiden tot significant minder hematologische toxiciteit door sparing van het beenmerg werd ook gerapporteerd in eerdere studies. Minder hematologische toxiciteit kan weer resulteren in verbeterde behandelingsresultaten door een verbeterde tolerantie voor chemotherapie. In de toekomst kunnen er verdere verbeteringen in radiotherapietechnieken worden verwacht met de implementatie van dagelijkse MR-geleide adaptieve radiotherapie, CT-gebaseerde aanpassing op basis van 4D cone-beam CT en snelle, geautomatiseerde treatmentplanningssoftware. Voor vaginale brachytherapie kan de toename in gebruik van CT of MRI resulteren in een betere visualisatie van het doelvolume en de risico-organen voorafgaand aan iedere fractie. Daarnaast kunnen, door gebruik te maken van een CT in de behandelkamer, brachytherapie-procedures efficiënter en patiëntvriendelijker worden uitgevoerd. Al deze ontwikkelingen kunnen leiden tot vermindering van marges, verhoogde precisie en verminderde belasting van de risico-organen en daarmee verminderde behandelingsgerelateerde toxiciteit en patiënt-gerapporteerde symptomen. Andere radiotherapiemodaliteiten, zoals protonenbestraling, worden momenteel geïntroduceerd voor gynaecologische maligniteiten en kunnen de dosis voor risico-organen, waaronder darm en beenmerg, nog verder verlagen. Met deze ontwikkelingen kan er in de toekomst minder toxiciteit en een hogere kwaliteit van leven door nauwkeurigere en beeldgestuurde adaptieve radiotherapie worden verwacht.

Discussie

In hoofdstuk 7 worden de belangrijkste uitkomsten van dit proefschrift samengevat en worden de toekomstperspectieven beschreven. Zoals eerder beschreven toonde de lange termijn resultaten van de PORTEC-2-studie geen verschil in lokale recidieven en overleving na vaginale brachytherapie versus uitwendige radiotherapie voor vrouwen met een hoog-intermediair risico endometriumcarcinoom. Aanvullende analyse van de combinatie van klinisch-pathologische en moleculaire risicofactoren toonde aan dat substantiële LVSI, *TP53*-mutatie en L1CAM-overexpressie sterk geassocieerd waren met het risico op recidief in het bekken en op afstand en verhoogde kankergerelateerde-sterfte. Patiënten met een van deze risicofactoren die werden behandeld met uitwendige radiotherapie bleken significant betere locoregionale controle te hebben dan degenen die werden behandeld met vaginale brachytherapie. Deze bevindingen illustreren dat binnen de groep met hoog-intermediair risico endometriumcarcinoom sommige vrouwen met risicofactoren als substantiële LVSI, L1CAM-overexpressie of p53abn tumor baat kunnen hebben bij uitwendige radiotherapie van het bekken in plaats van brachytherapie. Aan de andere kant kan brachytherapie bij gunstige kenmerken overbehandeling zijn. Deze rationale wordt momenteel onderzocht in de lopende PORTEC-4a studie. In deze studie krijgen vrouwen in de experimentele arm adjuvante behandeling op basis van hun geïntegreerde moleculaire profiel.

Retrospectief is een soortgelijke analyse gedaan in de PORTEC-3 populatie met een hoog risico endometriumcarcinoom. Resultaten toonde de volgende onderverdeling van de moleculaire groepen: 22% had een p53abn endometriumcarcinoom, 13% een *POLE*-tumor, 33% MMRd, en 32% NSMP endometriumcarcinoom. Met deze moleculaire onderverdeling werden opmerkelijke overlevingsverschillen waargenomen. Patiënten met een endometriumcarcinoom met een *POLE*-mutatie hadden een uitstekende prognose (98,0% recidiefvrije en algehele overleving zonder verschil tussen de studiearmen), terwijl degenen met een p53abn tumor een significant slechtere prognose hadden (48,0% en 54,0% recidiefvrije en algehele overleving). Verder had de subgroep met p53abn tumor het grootste voordeel van de toevoeging van chemotherapie met een absoluut verschil van 22,4% en 23,1% voor recidiefvrije en algehele overleving na 5 jaar, terwijl voor de MMRd-subgroep geen voordeel van toegevoegde chemotherapie werd waargenomen ten opzichte van alleen uitwendige radiotherapie. Binnen de NSMP-subgroep toonde de toevoeging van chemotherapie een trend voor verbeterde recidiefvrije overleving. De relatief kleine subgroep binnen de NSMP-groep met negatieve ER- en PR-receptoren bleek in een recent onderzoek een slechtere prognose te hebben en vaker een niet-endometrioïd histologisch type te zijn. Toekomstige uitdagingen blijven de verdere specificatie van risicokenmerken binnen de NSMP-subgroep en het definiëren van een optimale adjuvante behandeling voor elke

individuele endometriumcarcinoompatiënt op basis van de specifieke klinisch-pathologische en moleculaire risicofactoren van de patiënt.

Met de kennis die is opgedaan over moleculaire risicofactoren bij endometriumcarcinoom kan de behandelingsselectie worden verbeterd door deze risicofactoren te implementeren in de behandelrichtlijnen. Endometriumcarcinomen die p53abn zijn, zelfs wanneer het een vroeg stadium betreft, moeten worden beschouwd als endometriumcarcinoom met een hoog risico en derhalve wordt gecombineerde adjuvante uitwendige radiotherapie en chemotherapie geadviseerd, zoals onderzocht in de PORTEC-3 populatie en ook in een Deens cohort. De PORTEC-3 studie toonde 10% overlevingsvoordeel voor sereus type carcinomen van alle stadia met de toevoeging van chemotherapie, sereus type carcinomen die ongeveer de helft van alle p53abn endometriumcarcinomen omvatten. Wat het exacte voordeel van toegevoegde chemotherapie aan uitwendige radiotherapie zal zijn voor stadium I (vooral stadium IA) p53abn endometriumcarcinoom moet nog verder worden onderzocht.

RAINBO-programma

De kenmerken van de vier moleculaire groepen hebben geleid tot nieuwe gerichte behandelstrategieën. Het RAINBO-onderzoeksprogramma voor vrouwen met een hoog risico endometriumcarcinoom is gebaseerd op het moleculaire classificatie- en translationeel onderzoek binnen het TransPORTEC onderzoeksconsortium. Het RAINBO-programma bestaat uit vier verschillende onderzoeken die zich richten op elke verschillende moleculaire subgroep, met als overkoepelend doel het evalueren van de impact op overleving en kwaliteit van leven met gerichte behandelingen, en met een overkoepelende biobank voor verder translationeel onderzoek.

Binnen de RAINBO-p53-Red studie van het RAINBO-programma worden vrouwen met een p53abn endometriumcarcinoom gerandomiseerd tussen chemoradiotherapie versus chemoradiotherapie met de PARP remmer olaparib. PARP, of poly (ADP-ribose) polymerase, is betrokken bij de detectie van DNA-schade en de vorming van poly (ADP-ribose) ketens. Deze ketens spelen een rol in DNA-herstel. Verlies van PARP resulteert in persisterende enkelstrengs DNA-breuken en uiteindelijk in dubbelstrengs DNA-breuken. Normaal gesproken worden deze gerepareerd door homologe recombinatie of andere reparatiemechanismen zoals niet-homologe eindverbinding. Echter wordt bij 46% van de endometriumcarcinomen met een *TP53*-mutatie homologe recombinatie deficiëntie (HRd) gevonden. Responspercentages van 31-40% op PARP-remmers zijn gerapporteerd bij HRd-ovariumcarcinoom en BRCA-gemuteerde borstkanker. Derhalve lijkt chemoradiotherapie in combinatie met een PARP remmer een veelbelovende behandeloptie voor p53abn subgroep.

In de RAINBO-MMRd-green studie worden vrouwen met een stadium II tot III MMRd endometriumcarcinoom gerandomiseerd tussen uitwendige radiotherapie versus uitwendige radiotherapie met een checkpoint remmer (PD-L1 remmer durvalumab). Het endometriumcarcinoom met MMRd brengt een of meer van de MMR-eiwitten niet tot expressie, wat leidt tot de accumulatie van mismatches, deleties en instabiliteit. Vanwege de grote hoeveelheid aan mutaties is er een toename van PD-1 en PD-L1-expressie, wat deze tumoren aantrekkelijk maakt voor immuuncheckpointremmers. Eerdere onderzoeken hebben deze hypothese bevestigd en lieten responspercentages zien van 13-48% met checkpointremmers zoals nivolumab, pembrolizumab en dostarlimab bij vrouwen met recidiverende of gemetastaseerde hypergemuteerde tumoren, waaronder endometriumcarcinoom.

De NSMP-subgroep is een heterogene groep tumoren met een laag aantal mutaties, en omvat meestal graad 1 tot 2 endometrioïd type carcinomen. Binnen deze subklasse is ongeveer 85-90% hormoonreceptor-positief. Hormoonreceptorstatus bleek een belangrijke prognostische factor te zijn, en verlies van ER- of PR-expressie is gerelateerd aan graad 3 tumoren met een niet-endometrioïd type, overexpressie van L1CAM, substantiële LVSI en verminderde ziektevrije overleving. Analyse van de PORTEC-3 NSMP-subgroep toonde aan dat de grote meerderheid van de tumoren ER- en PR-positief waren. Hierdoor lijkt hormonale therapie een effectieve behandelstrategie. In de RAINBO-NSMP-Orange studie van het RAINBO-programma zal worden onderzocht of de toevoeging van hormonale therapie aan radiotherapie even effectief is als chemoradiotherapie, met significant minder bijwerkingen en betere kwaliteit van leven.

Zoals reeds eerder beschreven hebben vrouwen met een endometriumcarcinoom met *POLE*-mutatie een zeer gunstige prognose. Deze endometriumcarcinomen hebben extreem veel mutaties, waardoor er een verhoogde antitumorrespons door tumor-infiltrerende CD8+-lymfocyten wordt beschreven. Ook kunnen deze extreem gemuteerde cellen minder functioneren en minder goed delen. In tegenstelling tot het slecht gedifferentieerde microscopische uiterlijk van deze subgroep, is aangetoond dat deze tumoren een uitstekende prognose hebben, zowel met als zonder adjuvante behandeling. De-escalatie of zelfs weglaten van adjuvante behandeling zal daarom worden onderzocht bij vrouwen met een endometriumcarcinoom met een *POLE*-mutatie in de RAINBO-POLE-Blue studie van het RAINBO-programma.

Conclusie

In dit proefschrift wordt aangetoond dat geïndividualiseerde behandeling op basis van klinisch-pathologische en moleculaire kenmerken in ontwikkeling is en kan leiden tot betere selectie van behandeling en minder bijwerkingen. Vaginale brachytherapie is momenteel de beste

adjuvante behandeling voor vrouwen met een vroeg stadium (hoog-)intermediair risico endometriumcarcinoom, met beperkte toxiciteit. Het risico op recidief hangt sterk samen met risicofactoren als substantiële LVSI, L1CAM-overexpressie en *TP53*-mutatie. Voor vrouwen met deze risicofactoren moet adjuvante uitwendige radiotherapie in plaats van vaginale brachytherapie worden geadviseerd om de locoregionale controle en de recidiefvrije overleving te maximaliseren. Door gebruik te maken van een moleculair geïntegreerd risicoprofiel bij het bepalen van de adjuvante behandeling, kunnen de resultaten worden verbeterd en vrouwen onnodige adjuvante behandeling met bijwerkingen bespaard worden. Dit wordt momenteel onderzocht in zowel de PORTEC-4a- als de TAPER-studies. De komende jaren zullen de resultaten uitwijzen of introductie moleculaire risicofactoren in de adjuvante behandeling leidt tot minder behandeling, effectievere behandeling en betere kwaliteit van leven. Afgelopen jaren is de kennis over moleculaire risicofactoren bij het endometriumcarcinoom sterk vergroot. We weten meer over de prognostische waarde en de mogelijke therapeutische opties van deze risicofactoren. Studies naar adjuvante behandeling op basis van moleculaire veranderingen voor vrouwen met (hoog-)intermediair of hoog risico en recidiverend of gemetastaseerd endometriumcarcinoom zijn gaande. Daarnaast zijn de radiotherapietechnieken voor endometriumcarcinoom in de loop van de tijd verbeterd. Moderne radiotherapietechnieken hebben het vermogen om de omliggende gezonde weefsels steeds meer te sparen met vergelijkbare of verbeterde oncologische resultaten en minder behandelingsgerelateerde toxiciteit. Toekomstige ontwikkelingen op dit vlak zijn te verwachten met de komst van dagelijkse beeldgestuurde adaptieve radiotherapie en toename in gebruik van innovatieve modaliteiten die de dosis voor de risico-organen verminderen. Toekomstige radiotherapie-onderzoeken moeten adequate programma's voor kwaliteitsborging includeren in het studieprotocol om een uniforme en hoge kwaliteit behandeling te kunnen bereiken. Al deze ontwikkelingen zullen in de toekomst leiden tot betere resultaten en hoge(re) kwaliteit van leven voor vrouwen met een endometriumcarcinoom.

LIST OF PUBLICATIONS AND CONFERENCE PRESENTATIONS

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CURRICULUM VITAE

Bastiaan Gijsbert Wortman werd geboren op 4 juni 1991 te Alkmaar. In 2009 behaalde hij zijn Gymnasium diploma aan het Murmellius Gymnasium te Alkmaar, waarna hij begon met de studie Geneeskunde aan de Universiteit van Leiden. Tijdens de studie geneeskunde werd zijn interesse met name gewekt voor de specialismen oncologie en radiologie. Daarnaast is Bastiaan, in de wachttijd van de co-schappen, 6 maanden naar Spanje geweest om de Spaanse taal te leren in Granada, Valencia, Madrid en Barcelona. Met deze opgedane taalkennis heeft hij vervolgens stage gelopen op de afdeling neurologie van het Hospital Universitario in Valladolid, Spanje, en later heeft hij ook zijn coschap huisarts geneeskunde gelopen in Havana, Cuba. Aan het einde van de opleiding geneeskunde kwam hij voor het eerst in aanraking met het specialisme radiotherapie, tijdens zijn wetenschappelijke stage naar de waarde van upfront PA revisie binnen de PORTEC-3 studie (dit proefschrift), onder begeleiding van prof. dr. C.L. Creutzberg en dr. T. Bosse.

Na zijn afstuderen in 2016 is Bastiaan begonnen als arts-assistent bij de interne geneeskunde van het Tergooi Ziekenhuis in Hilversum/Blaricum. In 2017 is hij teruggekeerd naar het LUMC om te starten met de opleiding tot radiotherapeut-oncoloog (opleiders: prof. dr. C.L. Creutzberg, prof. dr. C.A.M. Marijnen, en later dr. I.M. Lips). Voor een extra uitdaging combineerde hij deze opleiding met het promotieonderzoek naar radiotherapie voor het endometriumcarcinoom onder begeleiding van prof. dr. C.L. Creutzberg, prof. dr. R.A. Nout en dr. T. Bosse. Zijn promotieonderzoek focuste zich op de onderwerpen radiotherapie voor hoog-intermediair risico endometriumcarcinoom, vaginale brachytherapie, uitwendige radiotherapie en (moleculaire) risicofactoren van het endometriumcarcinoom.

Inmiddels heeft Bastiaan de opleiding tot radiotherapeut-oncoloog afgerond en is hij werkzaam als radiotherapeut-oncoloog in het Catharina Ziekenhuis te Eindhoven met de aandachtsgebieden mamma-, urologische- en gynaecologische-oncologie.

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