Post Operative Radiation Therapy in Endometrial Carcinoma

Reducing Overtreatment
and
Improving Quality of Life

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Contents

1

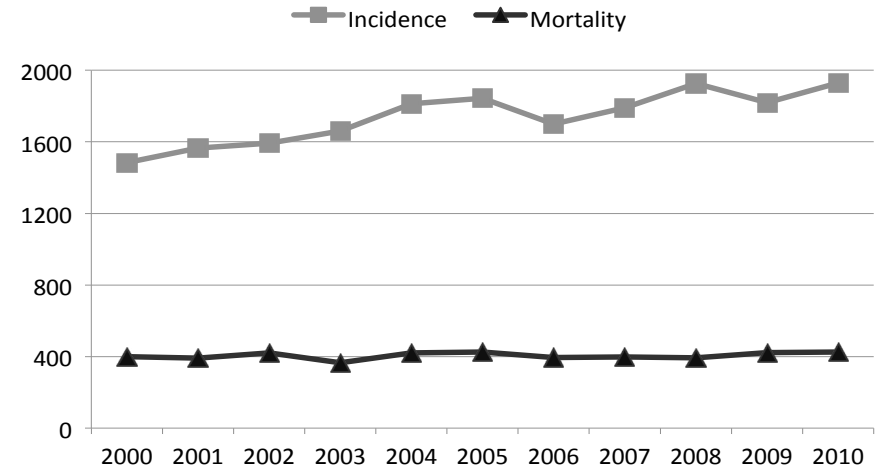
Introduction

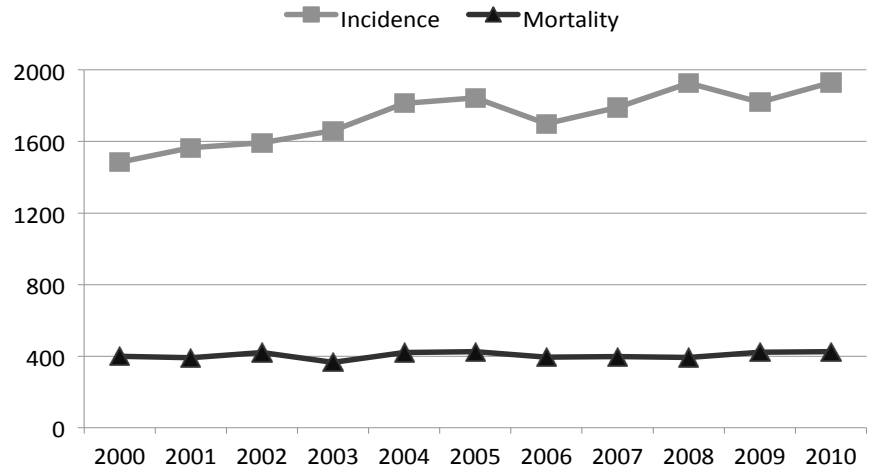
1.1 Epidemiology of endometrial cancer

Endometrial cancer (EC) is the most frequent gynaecologic malignancy in Western countries with incidence rates ranging between 15 and 25 per 100.000 women annually.[1,2] In the Netherlands, the incidence over the last decade was 16-19 per 100.000 women annually (European standardized rate). In 2010 there were 1930 new cases, 425 deaths and approximately 19.000 women alive after having been diagnosed and treated for EC during the previous 20 years in the Netherlands.[3] Due to the increased life expectancy and increasing age of the population, there has been an increase in the number of patients diagnosed with EC during the past decade.[4] Since mortality rates have remained stable in this period the prevalence has increased (Figure 1). The increasing numbers of long-term survivors stress the importance of potential long-term treatment related morbidities.

EC is typically a cancer of postmenopausal women between 50 and 85 years of age, with peak incidence between 65 and 80 years.4 The majority of patients present with early symptoms of postmenopausal vaginal blood loss, leading to diagnosis and treatment at an early stage when the disease is confined to the uterus.[5] In 1988, the International Federation of Obstetricians and Gynecologists (FIGO) has replaced clinical staging with a surgical-pathologic staging system, which has been updated in 2009 (Figure 2).[6,7] According to the 26th FIGO annual report, using the 1988 classification, 71% of patients presented with FIGO stage I; 12% with stage II; 14% stage III; and 3% of patients were diagnosed with stage IV disease. The reported 5-year survival rates are 80% for all patients, 85-90% for patients with stage I disease, 75-85% for stage II, 50-65% for stage III and 20-25% for stage IV.[8]

Figure 1. Netherlands Cancer Registry: Incidence, mortality and 10-year prevalence of endometrial cancer in the Netherlands.[3]





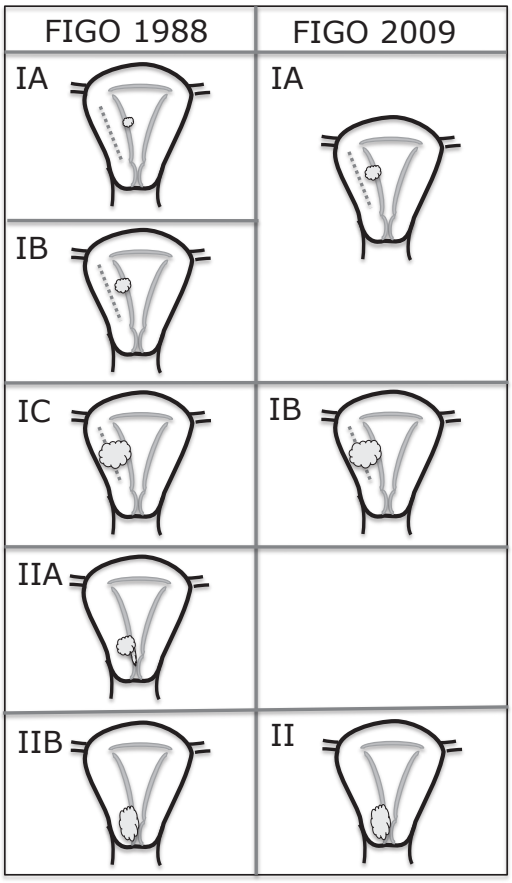


Figure 2.

FIGO 1988 staging
IA: limited to endometrium
IB: <50% myometrial invasion
IC: >50% myometrial invasion
IIA: endocervical glandular involvement
IIB: cervical stroma invasion
IIIA: Tumor invades the serosa of the corpus uteri and/or adnexae and/or positive peritoneal cytology
IIIB: Vaginal involvement
IIIC: Metastasis to pelvic and/or para-aortic lymph nodes
IVA: Tumor invades bladder and/or bowel mucosa
IVB: Distant metastasis

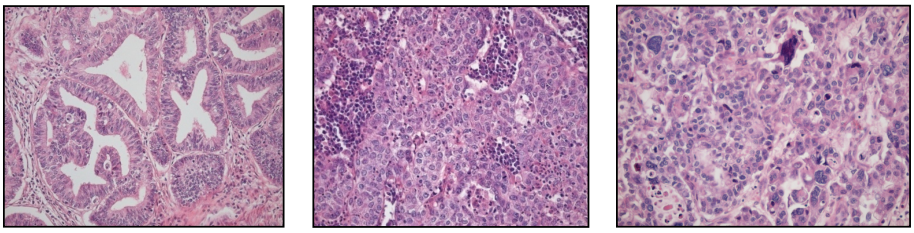
FIGO 2009 staging
IA: <50% myometrial invasion;
IB: >50% myometrial invasion
II: invasion of the cervical stroma;
IIIA: Tumor invades the serosa of the corpus uteri and/or adnexae
IIIB: Vaginal and/or parametrial involvement
IIIC: Metastasis to pelvic (C1) and/or para-aortic (C2) lymph nodes
IVA: Tumor invades bladder and/or bowel mucosa
IVB: Distant metastasis

Risk factors for the development of EC include those factors that are associated with prolonged exposure of the uterus to unopposed estrogens, such as anovulation, nulliparity, early menarche, late onset of menopause, obesity and exogenous (unopposed) estrogen or tamoxifen treatment.[9] In general, EC occurs in elderly women with a high prevalence of co-morbid conditions such as obesity, diabetes, cardiovascular disorders and arthropathy with associated use of medications, which can provide challenges with regard to the delivery of optimal treatment.[10] Less than 1-5% of EC are attributable to familial and hence potential hereditary genetic factors.[11,12] These are typically younger patients who develop EC as part of a Lynch syndrome, who have 60-70% life time risk for developing endometrial cancer.[13]

1.2 Pathology

Endometrial carcinoma arises in the endometrium, the glandular tissue that lines the inside of the cavum uteri. The most common histological type of endometrial cancer (80-85%) has a glandular growth pattern that shows a strong resemblance with normal endometrial glands, and is therefore called endometrioid endometrial cancer (EEC).[14] EEC is graded according to FIGO grading criteria, based on the percentage of solid growth and nuclear atypia (Figure 3).[6]

Figure 3. FIGO grading system: grade 1 tumors have 5% or less; grade 2 have 6% to 50% and grade 3 have more than 50% of an nonsquamoues or nonmorular solid growth pattern. A higher degree of nuclear atypia (in companson with the architectural grade) raises the grade of a G1 or G2 tumor by 1.



Glands | Solid growth | Nuclear atypia

Most EEC (80%) are well differentiated (grade 1) or intermediate grade tumors. Other histological subtypes are referred to as non-endometrioid endometrial cancers (NEEC) and among others include serous carcinoma (5%), and clear cell carcinoma (1-5%), which are considered high grade tumors.[14] Pre-malignant lesions commonly precede EEC and NEEC.[15] EEC usually develop in an estrogen rich environment, are often found in a background of endometrial hyperplasia and can be preceded by atypical endometrial hyperplasia. NEEC is often preceded by endometrial intraepithelial carcinoma (EIC), and found in a background of atrophic endometrium. Mesenchymal and mixed tumors, such as leiomyosarcoma, stromacelsarcoma and carcinosarcoma are rare uterine tumors and are seen as separate entities both from the pathogenetic and clinical point of view.[5,14] These are not further discussed in this thesis.

In 1983, Bokhman described two different types of endometrial cancer based on both clinical and pathological observations.[16] Patients with type I tumors (the majority of patients) showed signs of hypothalamopituitary and

ovarian hyperactivity resulting in hyperestrogenia, lipid and carbohydrate metabolic disturbances (prolonged duration of symptoms due to anovulatory uterine bleeding, hyperplasia, obesity, hyperlipidemia, diabetes mellitus and hypertension). Type II patients were usually older and characterized by the absence of endocrine-metabolic disturbances (short duration of symptoms, background of atrophic endometrium). Type I patients more often had superficial invasive well differentiated (low-grade EEC) tumors and a good prognosis, while type II patients more often had deep invasive high grade NEEC with a more aggressive clinical course.

Over the past decades different (epi)genetic alterations involved in type I and II carcinogenesis have been found (Table 1).[14,15,17-19]

Table 1. Biological markers involved in endometrial cancer with a focus on the distinction of Type I from Type II.

Marker	Function	Type I (%)	Type II (%)
ER/PR	Transcription factor	70-75	20-25
PTEN	Tumor suppressor	35-55	0-10
KRAS	Oncogene	15-25	0-10
PIK3CA	Oncogene	25-35	25-35
MSI*	DNA repair	20-30	0-5
ß-catenin	Oncogene	25-40	0-5
E-cadherin	Tumor suppressor	20-45	55-75
TP53	Tumor suppressor	5-10	80-90
CDKN2A	Tumor suppressor	10	10-40
ARID1a	Tumor suppressor	30-40	0-10
ERBB2	Oncogene	rare	20-80

*Defects in mismatch repair genes (i.e. MLH-1, MSH-2, MSH-6).

In type II cancers mutation of the tumor suppressor gene *TP53* seems to play a central role as it is found in 90% of the tumors.[20,21] Because *TP53* mutations are found both in the invasive and the intraepithelial precursor lesions, *TP53* loss is considered an early event in type II carcinogenesis.[21] Other characteristic alterations for type II tumors include mutation of the tumor suppressor gene *CDKN2A* (encoding for the tumor suppressor protein p16), and amplification of the oncogene *ERBB2* (encoding for the Human Epidermal Growth Factor Receptor 2, HER-2). For type I tumors there seems not to be a single specific genetic alteration which plays a major role in the carcinogenesis. Type 1 tumors are a heterogenous group of tumors in which different combinations of genetic alterations have been observed.[15,19] The main genetic alterations

known to drive type I (EEC) development are mutations in the tumor suppressor gene *PTEN* and in the oncogenes *KRAS*, *PIK3CA*, and *CTNNB-1* (ß-catenin).[15] *PTEN*, *KRAS* and *PIK3CA* converge in the PI3K-AKT signalling pathway, which has been implicated in nearly all aspects of tumor biology.[22,23] ß-catenin is a key component of the Wnt signaling pathway, interacting with the TCF/LEF family of transcription factors.[24,25] In addition micro-satellite instability (MSI), a marker for defects in mismatch repair genes, is found in 20-30% of the type I tumors.[26-28] The vast majority of tumors with MSI are sporadic tumors. It is estimated that less than 1-5% of endometrial carcinomas are caused by potential hereditary genetic factors such as Lynch syndrome.[11,12] In patients with sporadic MSI, silencing of the mismatch repair gene *MLH1* by promoter hypermethylation is the main cause of a mismatch repair deficiency.[29] In Lynch syndrome, MSI is caused by a germline mutation in one of the mismatch repair genes (most often *MLH1*, *MSH2* and *MSH6).*[30] *ARID1a* is a tumor suppressor gene that has recently been established in endometrial cancer and is involved in the SWI/SNF complex of chromatin remodeling. Loss of ARID1a expression has been found most frequent in endometrioid type tumors (30-40%) and clear cell histology (20%) and very rare in serous carcinoma.[31-33] Mutations in *PTEN*, *KRAS* and *ARID1a*, and nuclear accumulation of ß-catenin as a sign of activated Wnt signaling have been found in atypical endometrial hyperplasia, suggesting these are early events in type I carcinogenesis.[15,32] On the other hand, a small proportion (10-15%) of invasive type I EEC have a mutation in *TP53*, which is not seen in atypical hyperplasia, implying that this is a late event in type I carcinogenesis.[34,35]

Despite the observed differences in genetic alterations there remains overlap between type I and type II tumors, and heterogeneity within both types. For example *PIK3CA* mutations are found both in type I and type II EEC, and in type I tumors MSI is often found in absence of other genetic alterations which reflects the heterogeneity of tumors within this group.

1.3 Prognostic factors

Clinico-pathological prognostic factors for survival in patients with endometrial cancer have been well documented in numerous studies, of which the GOG#33 surgical staging study has been of major importance.[6] FIGO stage is (per definition) one of the most important prognostic factors.[8] Histologic subtype represents another major prognostic factor.[6,36] Endometrioid type endometrial cancer has a favorable prognosis compared to the far less common serous and clearcell cancer subtypes. The 5-year survival rate for EEC is 80-85%, compared to 50-55% for serous, and 60-65% for clearcell cancers. Other major prognostic factors include age, histological grade, depth of myometrial invasion and lymph vascular space invasion, which are further discussed in paragraph 1.5.
In addition to these clinicopathologic risk factors, several studies have investigated the prognostic capacity of genetic alterations involved in endometrial carcinogenesis.[17,27,34,35,37,38] The majority of studies indicate that expression of the estrogen and progesterone hormone receptors (DNA-binding transcription factors) and activation of the Wnt/ß-catenin signaling pathway and mutations in *CDH1* (encoding for the cell adhesion protein) are associated with a good prognosis, while mutation of *TP53*, *CDKN2A* and activation of the PI3K-AKT pathway are indicators of tumors with a more aggressive clinical course. Conflicting results have been reported with regard to the prognostic significance of MSI, mutations in *PTEN*, *KRAS* and amplification of *ERBB2*. Most studies were relative small, retrospective and included a heterogenous group of patients including both higher FIGO stages and a combination of endometrioid type and non-endometrioid type tumors. For these reasons genetic alterations are not yet used as prognostic factors in clinical practice.

1.4 Treatment of endometrial carcinoma

Surgery, consisting of total abdominal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy (TAH/TLH-BSO), is the mainstay of treatment. Already in 1878 Freund performed the first successful total abdominal hysterectomy for endometrial carcinoma.[39] Radiotherapy, either used as adjuvant therapy or as an alternative for operation in medically unfit patients, was well recognized around 1920.[40] During the first half of the 20th century

preoperative external beam radiotherapy or intrauterine brachytherapy followed by surgery were used as standard treatment.[41,42] However, when it became clear that at postoperative pathological evaluation most patients had low risk features, from 1970 onwards surgery with adjuvant radiotherapy tailored to prognostic factors gained interest, and became the standard treatment approach.[6] During the second half of the 20th century complication rates of the TAH-BSO procedure decreased due to advances in surgical techniques and perioperative care. With the development of laparoscopic surgical techniques, both laparoscopic-assisted vaginal hysterectomy and total laparoscopic hysterectomy have gained interest because of the faster postoperative recovery. These techniques were introduced in the 1990s for early stage disease, and studies since then have shown a decreased length of hospital stay, less pain, a faster resumption of daily activities and improved patient reported quality of life compared to the traditional TAH-BSO.[43-45]

The role of pelvic and para-aortic lymphadenectomy has been the subject of ongoing debate. Although formally the surgical/pathological FIGO staging is based on information with regard to lymph nodes, it is specified that the performance of a staging lymphadenectomy should be a clinical decision weighing the benefit of the additional information with regard to lymph node status against potential complications and long-term side effects associated with lymphadenectomy.[46,47] Two recent large randomised trials allocated patients to TAH-BSO with or without lymphadenectomy and found no benefit in overall and disease free survival, nor differences in rates and sites of recurrence, while lymphadenectomy was associated with higher rates of treatment related morbidity, especially lymphedema.[48,49] Since both trials predominantly included patients with intermediate risk EC, routine use of pelvic and para-aortic lymphadenectomy is not recommended in low and intermediate risk patients. Trials are being planned to investigate its role in high-risk (grade 3) EC.

1.5 Adjuvant treatment for endometrial cancer

Adjuvant treatment has increasingly been tailored to prognostic factors. Risk groups have been defined based on clinico-pathological risk factors (Table 2).[50,51] Approximately 55% of patients present with early stage, low-risk endometrial cancer. These patients have 95% probability of relapse-free survival without further treatment, and adjuvant radiation therapy is not indicated.

Table 2. Risk groups for adjuvant therapy.

Risk group		Criteria
Low risk		Endometrioid type, grade 1 or 2, without myometrial invasion
Intermediate risk	Low-intermediate risk	Endometrioid type, age <60 years, grade 1 or 2 with superficial (<50%) myometrial invasion or grade 3 without invasion, or grade 3 with superficial myometrial invasion without lymph vascular invasion
	High-intermediate risk	PORTEC: Endometrioid type, age ≥60 years, grade 1 or 2 with deep (≥50%) myometrial invasion or grade 3 with superficial invasion
		GOG#99: age ≥70 years and 1 of the following risk factors: deep myometrial invasion, grade 2 or 3, lymph vascular space invasion; or age 50-70 and 2 risk factors; or all ages and all risk factors
High risk		Endometrioid type, grade 3 and deep myometrial invasion Endometrioid type stage II-III Non-endometrioid high grade (serous or clearcell type) stage I-III

Four randomized trials have established the role of radiation therapy in intermediate risk stage I endometrial carcinoma (Table 3).[50-53] Conclusions are that pelvic radiotherapy provides a highly significant improvement of locoregional control (vaginal and/or pelvic), but without survival advantage, and at the cost of (predominantly mild) gastrointestinal toxicity. Therefore, the use of radiation therapy has been limited to patients at higher risk of locoregional recurrence to warrant the risk of treatment-associated morbidity in order to maximize local control and relapse-free survival.

Table 3. Randomized trials establishing the role of postoperative radiotherapy in intermediate risk endometrial cancer.

Trial (ref) acrual period	No. patients, eligibility	Surgery	Randomization	Locoregional recurrence	Survival	Severe complications
Norwegian[49] 1968–1974	540; Stage I	TAH-BSO	VBT vs VBT + EBRT	7% vs 2% at 5 years P < 0.01	89% vs 91% at 5 years P= NS	1% vs 1% gr 4/5
PORTEC-1[47] 1990–1997	714; IB grade 2–3 IC grade 1–2	TAH-BSO	NAT vs EBRT	14% vs 4% at 5 years P < 0.001	85% vs 81% at 5 years P= 0.31	3% GI at 5 years, (actuarial)
GOG#99[49] 1987–1995	392; Stage IB, IC Stage II (occult)	TAH-BSO and lymphadenectomy	NAT vs EBRT	12% vs 3% at 2 years P < 0.01	86% vs 92% at 4 years P= 0.56	8% GI at 2 years, (crude)
ASTEC/EN5[50] 1996–2005	905; Stage IAB g3, IC, Stage II, serous/cc	TAH-BSO ± lymphadenectomy	NAT vs EBRT	7%a vs 4% at 5 years P= 0.038	84% vs 84% at 5 years P= 0.98	3 vs 7% gr 3/4

cc: clear cell. TAH-BSO: total abdominal hysterectomy with bilateral salpingo-oophorectomy. VBT: vaginal brachytherapy. EBRT: pelvic external beam radiotherapy. GI: gastro-intestinal.

Both PORTEC-1 and GOG#99 trials established risk factors to better select patients at risk of recurrence within the intermediate risk group.[50,51] Using these risk factors (age, grade, depth of myometrial invasion and lymph vascular space invasion), in both trials devised a so-called high-intermediate risk (HIR) group was defined (Table 2). Patients with HIR features in the no-RT arm of the PORTEC-1 trial had a 10-year locoregional recurrence risk of 23%, compared to 5% in the RT group.[54] The locoregional recurrence rate in the low-intermediate risk patients was 5% at 5 years and there was no clinical relevant decrease with radiotherapy. In the GOG#99 trial, RT resulted in a reduction of 4-year isolated local relapse in their HIR group from 13% to 5%. The indication for RT is currently restricted to patients with HIR features. The implementation of these high-intermediate risk factors to select patients led to an important reduction in the indication for adjuvant radiotherapy in stage I patients.

Approximately 75% of the locoregional recurrences in PORTEC-1 patients who did not receive additional radiotherapy were located in the proximal vagina.[50] With vaginal brachytherapy the vaginal vault and scar area are treated locally, with decreased radiation exposure of the surrounding normal organs compared to EBRT (Figure 4). Most (retrospective) studies using postoperative vaginal brachytherapy alone have reported high rates of vaginal control (92-98%), using a variety of dose and fractionation schedules (Table 4).[55-64] However, most of these studies included mainly low-risk patients.

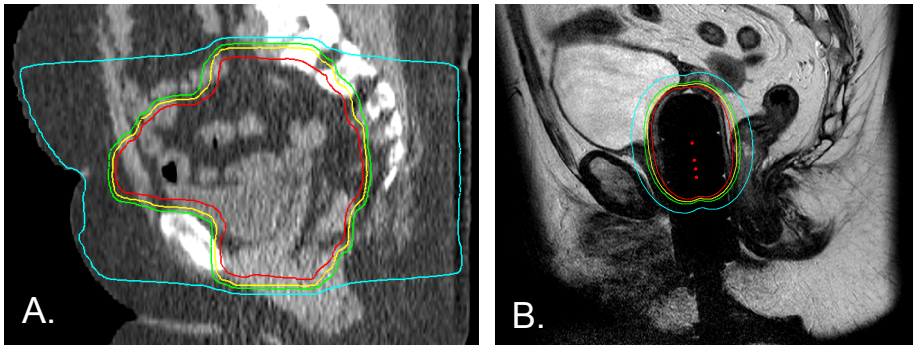


Figure 4. (A) Pelvic external beam radiotherapy dose distribution on CT in the sagittal midplane, in red 95% isodose of 46 Gy. (B) Vaginal brachytherapy using a 3.5 cm vaginal cylinder, dose distribution on MRI in the sagittal midplane, in red 100% isodose of 7 Gy at 0.5 cm distance of the applicator surface.

Table 4. Results of postoperative vaginal brachytherapy for endometrial cancer.

Author (ref) acrual period	No. patients, eligibility	Treatment	Vaginal recurrence	Locoregional recurrence	Survival	Severe complications
Institutional series including at least 100 patients						
Sorbe et al.[60] publ 1990	404; Stage I		0,7%	3,0%	92% OS at 5-years	6.9% significant
MacLeod et al.57 1985-1993	141; Stage I-IIIA	4 x 8.5 Gy at surface	1,4%	2,0%	91% OS at 5-years	no grade 3/4
Weiss et al.[61] 1987-1993	122; Stage I-II	3 x 7 Gy at surface	1,6%	4,1%	94% NED at 5-years	no grade 3/4
Eltabbakh et al.[55] 1958-1994	332; Stage IA grd 1-2	1 x 30 Gy LDR at surface	0,0%	0,6%	99% DFS at 5-years	2.1% grade 3/4
Petereit et al.[58] 1989-1997	191; Stage IA grd 1-2	2 x 16.2 Gy at surface ovoids	0,0%	0,5%	95% OS at 5-years	0.5% grade 4
Anderson et al.[53] 1990-1996	102; Stage I	3 x 5 Gy at 0.5 cm	1,0%	1,9%	84% OS at 5-years	no grade 3/4
Horowitz et al.[56] 1989-1999	164; Stage I-II	3 x 7Gy at 0.5 cm	1,2%	0,6%	87% OS at 5-years	no grade 3/4
Alektiar et al.[52] 1987-2002	382; Stage I-II	3 x 7Gy at 0.5 cm	0,8%	0,0%	93% OS at 5-years	0.5% grd 3/0.3% grd 4
Solhjem et al.[59] 1998-2004	100; Stage I grd 2-3 and IB grd 1-2 if >2cm	3 x 7Gy at 0.5 cm	0,0%	0,0%	98% OS at 3-years	no grade 3/4
Ataham et al.[54] 1994-2005	128; Stage I	5 x 5.5 Gy at 0.5 cm	0,0%	1,6%	96% OS at 5-years	no grade 3/4

LDR: low dose rate. VBT: vaginal brachytherapy. NAT: no adjuvant therapy. NED: no evidence of disease. OS: overall survival

The randomized PORTEC-2 trial was initiated to investigate if vaginal brachytherapy would be equally effective as pelvic external beam radiotherapy in reducing vaginal recurrence in endometrial cancer patients with HIR features, with less treatment related toxicity and better quality of life. The outcomes of this trial are discussed in the following chapters of this thesis.

External beam pelvic radiotherapy remained indicated only for patients with high-risk and advanced stage endometrial carcinoma to maximize pelvic control. However, distant metastases determine the inferior outcome for high-risk patients, with reported 5-year overall survival rates of 60-65%.[65] Two randomised trials comparing pelvic external beam radiotherapy with adjuvant chemotherapy in high risk patients did not show an improvement in overall or disease free survival.[66,67] Recently, the results of the combined analysis of the NSGO 9501 / EORTC 55991 and MaNGO-ILIADE III trials have been published.[68] In both trials postoperative external beam radiotherapy was randomly compared to radiotherapy with adjuvant chemotherapy (4 cycles of platinum-based chemotherapy given either before or after radiation therapy), showing a significantly improved 5-year progression free survival of 78% vs 69%, p=0.009, but only a trend for improved overall survival (82% vs 75%, p=0.07). Current ongoing trials (PORTEC-3, GOG#249 and GOG#258) are investigating the role of chemotherapy in combination with radiotherapy, or replacing radiotherapy for high risk and advanced stage endometrial cancer patients.

A wide range of systemic therapies have been evaluated in patients with distant metastasis or recurrent disease. Hormonal treatment is an attractive option, because this treatment is relative well tolerated compared to chemotherapy. Progestins show the highest response rates in patients with progesterone receptor positive and/or low grade EC, with response rates ranging between 20-35% and a median response duration of 4 months.[69] However, most patients with metastatic disease have grade 3, hormone receptor negative disease. Paclitaxel- and platinum-based combination chemotherapy is currently the most effective treatment. The addition of paclitaxel to doxorubicin and cisplatinum was associated with improved response rates (50%) and survival, however at the cost of increased toxicity.[70] The combination of paclitaxel with carboplatin is potentially less toxic, and has been shown to be at least equally effective in phase 2 studies.[71,72] Premliminary results of the GOG#209 trial in which 1300

women were randomized between carboplatin and paclitaxel versus paclitaxel-doxorubicin-cisplatinum confirm the equivalence with an identical progression free and overall survival, together with reduced toxicity for patients treated with carboplatin-paclitaxel.[73] Finally, several targeted therapies such as MTOR inhibitors, and (multitarget) protein kinases are currently being tested for their efficacy in ongoing clinical trials.[37,74]

1.6 Aims and outline of this thesis

The main purpose of the Post Operative Radiotherapy in Endometrial Carcinoma (PORTEC) trials has been to provide evidence with regards to risks (short and long-term treatment related morbidity) and benefits (disease control) of adjuvant radiotherapy, with the ultimate goal to improve the overall outcome and quality of life of endometrial cancer patients.

After publication of the results of the PORTEC-1 trial, in the Netherlands and many other countries postoperative radiotherapy became restricted to patients with high-intermediate risk features. This has led to a significant decrease of overtreatment of endometrial cancer patients. Because the majority (75%) of the locoregional recurrences in the no additional therapy arm of the trial were located in the vagina, the rationale of the subsequent randomized trial (PORTEC-2) was to compare the efficacy of vaginal brachytherapy and external beam pelvic radiotherapy, to determine which treatment provides optimal local control with least morbidity and best quality of life for patients with high-intermediate risk endometrial cancer.

This thesis describes results of the first and second PORTEC trials. The first aim of this thesis was to establish the role of postoperative vaginal brachytherapy as compared to pelvic external beam radiotherapy in terms of efficacy, treatment related toxicity, patient-reported symptoms and health related quality of life in the PORTEC-2 trial. The second aim of this thesis was to analyze the very long-term outcomes of the PORTEC-1 trial, including an analysis of patient reported symptoms and health related quality of life of long-term survivors. The third aim of this thesis was to investigate whether adverse molecular prognostic factors established by analysis of genetic alterations in the main pathways involved in endometrioid type (EEC) carcinogenesis can improve the currently used method of risk assessment based on clinicopathological factors, with

the ultimate goal to further reduce both over- and undertreatment. **Chapter 2** describes the short-term health related quality of life reported by patients in the PORTEC-2 trial during the first two years after randomization. In **Chapter 3** the final results of the PORTEC-2 trial are presented, with analysis of the primary (vaginal recurrence) and secondary (locoregional, distant recurrence, overall and disease free survival and toxicity) endpoints at a median follow-up of 45 months, including central pathology review.

Chapter 4 describes the very long-term health related quality of life (HRQL) of patients who participated in the PORTEC-1 trial, 10-12 years after treatment. General HRQL of patients in both arms of the trial was compared to an age-matched norm population. In **Chapter 5** the 15-year outcomes of the PORTEC-1 trial are analyzed, focusing on the role of high-intermediate risk criteria for radiotherapy treatment selection, and the long-term risk of developing second cancers.

Chapter 6 describes the long-term health related quality of life of patients in the PORTEC-2 trial with a median follow-up of 65 months, including comparison with an age-matched Dutch norm population.

Chapter 7 describes the analysis of genetic alterations in the main pathways involved in endometrioid type (EEC) carcinogenesis (PI3K-AKT, Wnt/β-catenin, P53-pathway activation and MSI) in formalin fixed paraffin embedded primary tumor samples of 65 patients that were selected from the PORTEC-2 trial. Both by uni- and multivariate analysis, the prognostic capacity of alternations in these individual pathways were tested as well as the prognostic impact of combined alternations in multiple carcinogenic pathways.

Chapter 8 provides a general discussion of the results, focusing on current issues and future directions.

References

1. Curado. M. P. E, B., Shin. H.R., Storm. H., Ferlay. J., Heanue. M. and Boyle. P., eds. Cancer Incidence in Five Continents, Vol. IX. IARC Scientific Publications No. 160, Lyon, IARC. 2007.
2. Bray F, Loos AH, Oostindier M, Weiderpass E. Geographic and temporal variations in cancer of the corpus uteri: incidence and mortality in pre- and postmenopausal women in Europe. Int.J.Cancer. 2005;117(1):123-131.
3. Registry NC. *www.kankerregistratie.nl* 1989-2010 based on April 2011 NCR data submission, posted to the NCR web site 2011.
4. Bray F, Dos SSI, Moller H, Weiderpass E. Endometrial cancer incidence trends in Europe: underlying determinants and prospects for prevention. Cancer Epidemiol. Biomarkers Prev. 2005;14(5):1132-1142.
5. Rose PG. Endometrial carcinoma. N.Engl.J.Med. 1996;335(9):640-649.
6. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer. 1987;60(8 Suppl):2035-2041.
7. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. May 2009;105(2):103-104.
8. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. Nov 2006;95 Suppl 1:S105-143.
9. Gambrell RD, Jr., Bagnell CA, Greenblatt RB. Role of estrogens and progesterone in the etiology and prevention of endometrial cancer: review. American journal of obstetrics and gynecology. Jul 15 1983;146(6):696-707.
10. Modesitt SC, van Nagell JR, Jr. The impact of obesity on the incidence and treatment of gynecologic cancers: a review. Obstetrical & gynecological survey. Oct 2005;60(10):683-692.
11. Parazzini F, La Vecchia C, Moroni S, Chatenoud L, Ricci E. Family history and the risk of endometrial cancer. International journal of cancer. Journal international du cancer. Nov 15 1994;59(4):460-462.
12. Gruber SB, Thompson WD. A population-based study of endometrial cancer and familial risk in younger women. Cancer and Steroid Hormone Study Group. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. Jun 1996;5(6):411-417.
13. Vasen HF, Wijnen JT, Menko FH, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. Gastroenterology. Apr 1996;110(4):1020-1027.

14. Silverberg S.G. MGL, Kurman R.J. Tumors of the Uterine Corpus. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. Lyon: IARCPress; 2003:217-257.
15. Hecht JL, Mutter GL. Molecular and pathologic aspects of endometrial carcinogenesis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Oct 10 2006;24(29):4783-4791.
16. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol.Oncol. 1983;15(1):10-17.
17. Engelsen IB, Akslen LA, Salvesen HB. Biologic markers in endometrial cancer treatment. APMIS. 2009;117(10):693-707.
18. Lax SF, Kurman RJ. A dualistic model for endometrial carcinogenesis based on immunohistochemical and molecular genetic analyses. Verhandlungen der Deutschen Gesellschaft fur Pathologie. 1997;81:228-232.
19. Samarnthai N, Hall K, Yeh IT. Molecular profiling of endometrial malignancies. Obstetrics and gynecology international. 2010;2010:162363.
20. Sherman ME, Bur ME, Kurman RJ. p53 in endometrial cancer and its putative precursors: evidence for diverse pathways of tumorigenesis. Human pathology. Nov 1995;26(11):1268-1274.
21. Tashiro H, Isacson C, Levine R, Kurman RJ, Cho KR, Hedrick L. p53 gene mutations are common in uterine serous carcinoma and occur early in their pathogenesis. The American journal of pathology. Jan 1997;150(1):177-185.
22. Oda K, Okada J, Timmerman L, et al. PIK3CA cooperates with other phosphatidylinositol 3'-kinase pathway mutations to effect oncogenic transformation. Cancer Res. 2008;68(19):8127-8136.
23. Shaw RJ, Cantley LC. Ras, PI(3)K and mTOR signalling controls tumour cell growth. Nature. May 25 2006;441(7092):424-430.
24. Moreno-Bueno G, Hardisson D, Sanchez C, et al. Abnormalities of the APC/beta-catenin pathway in endometrial cancer. Oncogene. Nov 14 2002;21(52):7981-7990.
25. Scholten AN, Creutzberg CL, van den Broek LJ, Noordijk EM, Smit VT. Nuclear beta-catenin is a molecular feature of type I endometrial carcinoma. J.Pathol. 2003;201(3):460-465.
26. Black D, Soslow RA, Levine DA, et al. Clinicopathologic significance of defective DNA mismatch repair in endometrial carcinoma. J.Clin.Oncol. 2006;24(11):1745-1753.
27. Mackay HJ, Gallinger S, Tsao MS, et al. Prognostic value of microsatellite instability (MSI) and PTEN expression in women with endometrial cancer: results from studies of the NCIC Clinical Trials Group (NCIC CTG). Eur.J.Cancer. 2010;46(8):1365-1373.
28. Zighelboim I, Goodfellow PJ, Gao F, et al. Microsatellite instability and epigenetic inactivation of MLH1 and outcome of patients with endometrial carcinomas of the endometrioid type. J.Clin.Oncol. 2007;25(15):2042-2048.
29. Horowitz N, Pinto K, Mutch DG, et al. Microsatellite instability, MLH1 promoter methylation, and loss of mismatch repair in endometrial cancer and concomitant atypical hyperplasia. Gynecologic oncology. Jul 2002;86(1):62-68.

30. Wijnen J, de Leeuw W, Vasen H, et al. Familial endometrial cancer in female carriers of MSH6 germline mutations. Nature genetics. Oct 1999;23(2):142-144.
31. Guan B, Mao TL, Panuganti PK, et al. Mutation and loss of expression of ARID1A in uterine low-grade endometrioid carcinoma. The American journal of surgical pathology. May 2011;35(5):625-632.
32. Werner HM, Berg A, Wik E, et al. ARID1A loss is prevalent in endometrial hyperplasia with atypia and low-grade endometrioid carcinomas. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. Oct 19 2012.
33. Wiegand KC, Lee AF, Al-Agha OM, et al. Loss of BAF250a (ARID1A) is frequent in high-grade endometrial carcinomas. The Journal of pathology. Jul 2011;224(3):328-333.
34. Catasus L, Gallardo A, Cuatrecasas M, Prat J. Concomitant PI3K-AKT and p53 alterations in endometrial carcinomas are associated with poor prognosis. Mod. Pathol. 2009;22(4):522-529.
35. Prat J, Gallardo A, Cuatrecasas M, Catasus L. Endometrial carcinoma: pathology and genetics. Pathology. Feb 2007;39(1):72-87.
36. Abeler VM, Kjorstad KE. Endometrial adenocarcinoma in Norway. A study of a total population. Cancer. Jun 15 1991;67(12):3093-3103.
37. Dedes KJ, Wetterskog D, Ashworth A, Kaye SB, Reis-Filho JS. Emerging therapeutic targets in endometrial cancer. Nat.Rev.Clin.Oncol. 2011;8(5):261-271.
38. Samarnthai N, Hall K, Yeh IT. Molecular profiling of endometrial malignancies. Obstet.Gynecol.Int. 2010;2010:162363.
39. WA F. A new method for extirpation of the whole uterus. berl.klin.wochenschr. 1878;15:417-418.
40. Heyman J. The radiotherapeutic treatment of cancer corporis uteri. The British journal of radiology. Mar 1947;20(231):85-91.
41. Del Regato JA, Chahbazian CM. External pelvic irradiation as a preoperative surgical adjuvant in treatment of carcinoma of the endometrium. The American journal of roentgenology, radium therapy, and nuclear medicine. Jan 1972;114(1):106-109.
42. Greven KM, Corn BW. Endometrial cancer. Current problems in cancer. Mar-Apr 1997;21(2):65-127.
43. Malzoni M, Tinelli R, Cosentino F, et al. Total laparoscopic hysterectomy versus abdominal hysterectomy with lymphadenectomy for early-stage endometrial cancer: a prospective randomized study. Gynecologic oncology. Jan 2009;112(1):126-133.
44. Mourits MJ, Bijen CB, Arts HJ, et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. The lancet oncology. Aug 2010;11(8):763-771.
45. Janda M, Gebski V, Brand A, et al. Quality of life after total laparoscopic hysterectomy versus total abdominal hysterectomy for stage I endometrial cancer (LACE): a randomised trial. The lancet oncology. Aug 2010;11(8):772-780.
46. Shepherd JH. Revised FIGO staging for gynaecological cancer. Br.J.Obstet.Gynaecol. 1989;96(8):889-892.

47. Wolfson AH, Sightler SE, Markoe AM, et al. The prognostic significance of surgical staging for carcinoma of the endometrium. Gynecologic oncology. May 1992;45(2):142-146.
48. Benedetti PP, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J.Natl.Cancer Inst. 2008;100(23):1707-1716.
49. Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet. 2009;373(9658):125-136.
50. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000;355(9213):1404-1411.
51. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol.Oncol. 2004;92(3):744-751.
52. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet.Gynecol. 1980;56(4):419-427.
53. Blake P, Swart AM, Orton J, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet. 2009;373(9658):137-146.
54. Scholten AN, van Putten WL, Beerman H, et al. Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int.J.Radiat.Oncol.Biol.Phys. 2005;63(3):834-838.
55. Alektiar KM, Venkatraman E, Chi DS, Barakat RR. Intravaginal brachytherapy alone for intermediate-risk endometrial cancer. Int.J.Radiat.Oncol.Biol.Phys. 2005;62(1):111-117.
56. Anderson JM, Stea B, Hallum AV, Rogoff E, Childers J. High-dose-rate postoperative vaginal cuff irradiation alone for stage IB and IC endometrial cancer. Int.J.Radiat. Oncol.Biol.Phys. 2000;46(2):417-425.
57. Atahan IL, Ozyar E, Yildiz F, et al. Vaginal high dose rate brachytherapy alone in patients with intermediate- to high-risk stage I endometrial carcinoma after radical surgery. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. Nov-Dec 2008;18(6):1294-1299.
58. Eltabbakh GH, Piver MS, Hempling RE, Shin KH. Excellent long-term survival and absence of vaginal recurrences in 332 patients with low-risk stage I endometrial adenocarcinoma treated with hysterectomy and vaginal brachytherapy without formal staging lymph node sampling: report of a prospective trial. Int.J.Radiat. Oncol.Biol.Phys. 1997;38(2):373-380.

59. Horowitz NS, Peters WA, III, Smith MR, Drescher CW, Atwood M, Mate TP. Adjuvant high dose rate vaginal brachytherapy as treatment of stage I and II endometrial carcinoma. Obstet.Gynecol. 2002;99(2):235-240.
60. MacLeod C, Fowler A, Duval P, et al. High-dose-rate brachytherapy alone post-hysterectomy for endometrial cancer. International journal of radiation oncology, biology, physics. Dec 1 1998;42(5):1033-1039.
61. Petereit DG, Tannehill SP, Grosen EA, Hartenbach EM, Schink JC. Outpatient vaginal cuff brachytherapy for endometrial cancer. Int.J.Gynecol.Cancer. 1999;9(6):456-462.
62. Solhjem MC, Petersen IA, Haddock MG. Vaginal brachytherapy alone is sufficient adjuvant treatment of surgical stage I endometrial cancer. Int.J.Radiat.Oncol.Biol. Phys. 2005;62(5):1379-1384.
63. Sorbe BG, Smeds AC. Postoperative vaginal irradiation with high dose rate afterloading technique in endometrial carcinoma stage I. International journal of radiation oncology, biology, physics. Feb 1990;18(2):305-314.
64. Weiss E, Hirnle P, Arnold-Bofinger H, Hess CF, Bamberg M. Adjuvant vaginal high-dose-rate afterloading alone in endometrial carcinoma: patterns of relapse and side effects following low-dose therapy. Gynecol.Oncol. 1998;71(1):72-76.
65. Creutzberg CL, van Putten WL, Warlam-Rodenhuis CC, et al. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial. J.Clin.Oncol. 2004;22(7):1234-1241.
66. Maggi R, Lissoni A, Spina F, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. British journal of cancer. Aug 7 2006;95(3):266-271.
67. Susumu N, Sagae S, Udagawa Y, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. Gynecologic oncology. Jan 2008;108(1):226-233.
68. Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur.J.Cancer. 2010;46(13):2422-2431.
69. Decruze SB, Green JA. Hormone therapy in advanced and recurrent endometrial cancer: a systematic review. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. Sep-Oct 2007;17(5):964-978.
70. leming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Jun 1 2004;22(11):2159-2166.

71. Hoskins PJ, Swenerton KD, Pike JA, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Oct 15 2001;19(20):4048-4053.
72. Scudder SA, Liu PY, Wilczynski SP, et al. Paclitaxel and carboplatin with amifostine in advanced, recurrent, or refractory endometrial adenocarcinoma: a phase II study of the Southwest Oncology Group. Gynecologic oncology. Mar 2005;96(3):610-615.
73. Miller D, Filiaci V, Flemming G. Randomized phase III noninferiority trial of first-line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study; Late-Breaking Abstract 1. SGO. Vol 125: Gynecological Oncology; 2012:771-773.
74. Slomovitz BM, Lu KH, Johnston T, et al. A phase 2 study of the oral mammalian target of rapamycin inhibitor, everolimus, in patients with recurrent endometrial carcinoma. Cancer. Dec 1 2010;116(23):5415-5419.

2

Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial

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Abstract

Purpose: Studies on quality of life (QOL) among women with endometrial cancer have shown that patients who undergo pelvic radiotherapy report lower role functioning and more diarrhea and fatigue. In the Post Operative Radiation Therapy in Endometrial Cancer (PORTEC) trial endometrial carcinoma patients were randomly assigned to receive external beam radiotherapy (EBRT) or vaginal brachytherapy (VBT). QOL was evaluated using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and subscales from the prostate cancer module, PR-25, and the ovarian cancer module, OV-28.

Patients and Methods: PORTEC-2 accrued 427 patients between 2002 and 2006, of whom 214 were randomly assigned to EBRT and 213 were randomly assigned to VBT. Three-hundred forty-eight patients (81%) were evaluable for QOL. QOL outcomes were analyzed at a median follow-up of 2 years.

Results: At baseline, after surgery, patient functioning was at the lowest level, and it increased during and after radiotherapy to reach a plateau after 12 months. Patients in the VBT group reported better social functioning ($p<0.002$) and lower symptom scores for diarrhea, fecal leakage, the need to stay close to the toilet, and limitation in daily activities because of bowel symptoms ($p<0.001$). At baseline, 15% of patients were sexually active; this increased significantly to 39% during the first year ($p<0.001$). Sexual functioning and symptoms did not differ between the treatment groups.

Conclusions: Patients who received EBRT reported significantly higher levels of diarrhea and bowel symptoms. This resulted in a higher need to remain close to a toilet and, as a consequence, more limitation of daily activities because of bowel symptoms, and decreased social functioning. Vaginal brachytherapy provides a better QOL, and should be the preferred treatment from a QOL perspective.

Introduction

Endometrial carcinoma is the most common gynecological malignancy among postmenopausal women in western countries.[1] Most patients are diagnosed at an early stage, and surgery, which consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy is the cornerstone of treatment.

Randomized trials on postoperative radiotherapy in endometrial carcinoma have shown that pelvic external-beam radiotherapy (EBRT) significantly reduced the rate of locoregional relapse. However, reduction of relapse did not translate into a survival benefit, and was achieved at the cost of more (predominantly mild) gastro intestinal toxicity.[2-7]

As a result of the first Post Operative Radiation Therapy in Endometrial Cancer (PORTEC) trial, the indication for radiotherapy was abandoned in the Netherlands for patients with a very low risk of locoregional recurrence.3 For the remaining so-called 'high-intermediate risk' patients (ie, age 60 years or older and stage IC grades 1 or 2, or stage IB grade 3) the benefit in terms of locoregional control (ie,19% locoregional relapse without radiotherapy vs. 5% with EBRT) and disease-free survival was considered to outweigh the risks in terms of treatment-related toxicity. As most (75%) locoregional relapses were located in the vagina, the multicenter, randomized, PORTEC-2 trial was initiated to investigate if vaginal brachytherapy (VBT) would be equally effective in reducing the risk of locoregional recurrence, while at the same time reducing treatment-related toxicity and improving health-related quality of life (HRQOL).

Little is known about HRQOL and the impact of adjuvant radiotherapy on HRQOL in endometrial cancer survivors. All studies are retrospective, most are quite small and have low questionnaire return rates (<40%).[8-12] One retrospective study with an adequate return rate (75%) found that EBRT was negatively associated with vitality and physical and social well-being, but scores of patients treated both with or without radiotherapy were similar to those of an age-matched population.[13] Although patient-perceived HRQOL is

an important factor to be used in the decision making process, whether or not postoperative radiotherapy should be recommended, there is a clear lack of data on HRQOL among patients with endometrial cancer.

The aim of this analysis was to investigate short-term HRQOL of patients with high-intermediate risk endometrial carcinoma treated in the PORTEC-2 trial and to evaluate the impact of EBRT compared with VBT on patient-perceived HRQOL.

Tabel 1. Patient characteristics of responders and non-responders

	Responders (n=348)					**Non-responders** (n=79)		
	EBRT (n=166)		**VBT** (n=182)					
	No. of Patients	%	No. of Patients	%	*P*-value‡	No. of Patients	%	*P*-value*
Age, years								
mean	69,5		70,1		0,45	71,3		0,16
range	52-88		46-86			52-89		
<60 years	7	4,2	6	3,3	0,29	3	3,8	0,33
≥60 years	159	95,8	176	96,7		75	96,2	
FIGO-stage					0,73			0,99
1B	11	6,1	13	7,2		8	9,2	
1C	137	82,9	147	80,7		58	75	
2A	18	11	22	12,2		9	11,8	
Histologic Grade					0,83			0,42
Grade 1	77	46,4	89	48,9		36	46,1	
Grade 2	78	47	79	43,4		34	43,4	
Grade 3	11	6,6	14	7,7		9	10,5	
KPS					0,18			0,10
0	118	71,1	119	65,4		61	78,2	
1	47	28,3	59	32,4		16	20,5	
2	1	0,6	4	2,2		1	1,3	
Comorbidity								
IBD	2	1,2	2	1,1	0,93	2	2,6	0,34
Diabetes	19	11,4	31	17	0,14	12	15,4	0,82
Hypertension	61	37	63	34,8	0,68	26	33,3	0,68
Cardiovascular	38	23	42	23,1	0,99	18	23,4	0,95
Other	24	14,5	28	15,5	0,79	14	17,9	0,51

EBRT: external beam radiotherapy; VBT: vaginal brachytherapy

KPS: Karnofski Performance Score; IBD: inflammatory bowel disease

FIGO: International Federation of Gynaecology and Obstetrics

‡: *P*-value for comparison EBRT vs. VBT

*: *P*-value for comparison responders vs. non-responders

Patients and Methods

Patient selection and study design of the PORTEC-2 trial

The PORTEC-2 trial was a multicenter, randomized trial that was conducted throughout the Netherlands to compare EBRT and VBT. Surgery consisted of total abdominal hysterectomy and bilateral salpingo-oophorectomy; clinically suspicious pelvic and/or periaortic lymph nodes were removed, but no routine lymphadenectomy was performed. The diagnosis of endometrial carcinoma, grade, histological subtype and depth of myometrial invasion were made by the regional pathologist. International Federation of Gynecology and Obstetrics 1988 staging was assigned on the basis of surgical and pathological findings.[14] Patients were eligible for the study if they had one of the following combinations of age and postoperative International Federation of Gynecology and Obstetrics stage: age ≥60 years and stage 1C grade 1 or 2, or stage 1B grade 3 disease; or any age and stage 2A disease (except grade 3 disease with >50% myometrial invasion). All patients had a WHO-performance score of ≤2. Written informed consent was obtained from all patients. The protocol was approved by the Dutch Cancer Society and the medical ethics committees of all participating centers.

EBRT was given to a total dose of 46 Gy in 2-Gy daily fractions, and five fractions were given per week. VBT was delivered to the upper half of the vagina using a vaginal cylinder. High-dose-rate (HDR; 90% of patients) and low-dose-rate (LDR; 10% of patients) schedules were used, aiming at an equivalent of 45-50 Gy to the vaginal mucosa with HDR schedules of 21 Gy at 5-mm depth, given in 3 fractions of 7 Gy, each 1 week apart; and LDR schedules of 30 Gy at 5-mm depth, in one session at 0.50 Gy/hr.

The primary endpoint was 5-year vaginal relapse rate (VRR) as cumulative incidence, with death as a competing risk.[15] Secondary endpoints were HRQOL, treatment-related toxicity, pelvic lymph node and distant relapse rates, and overall survival. To detect a clinical relevant difference in VRR with sufficient precision, a total of 400 patients were required during an accrual period of 4

years. For evaluation of HRQOL this sample size would be more than sufficient to obtain significant and clinically relevant results, even when taking dropout into account.

QOL Assessment

Cancer-specific HRQOL was measured with the European Organization for Research and Treatment of Cancer C30 questionnaire (EORTC QLQ-C30, version 3.0).[16] The EORTC QLQ-C30 is a multidimensional, cancer-specific quality of life questionnaire developed for repeated assessments in clinical trials and has been found valid and reliable in various cancer populations. The QLQ-C30 questionnaire contains five functional scales (physical, cognitive, emotional, social and role functioning), a global health status/quality of life scale, three symptom scales (pain, fatigue and nausea/vomiting), and six single items assessing additional symptoms (dyspnea, insomnia, loss of appetite, constipation, diarrhea) and perceived financial impact.

Although an endometrial cancer module is currently being developed by the EORTC Quality of Life Group, no endometrial cancer-specific symptom questionnaire was available when PORTEC-2 was active. With approval of the EORTC Quality of Life Group, relevant subscales from existing published EORTC modules, which had previously undergone psychometric evaluation and validation, were combined into a symptom module for this study. The subscales for bowel and bladder symptoms from the prostate cancer module (PR-25) and the subscale for sexual functioning and symptoms from the ovarian cancer module (OV-28) were used.[17, 18]

For all items, Likert-type response scales were used, and the response scale ranged from 4 to 7 points. All subscales and individual-item responses were linearly converted to 0 to 100 scales. A higher score for a functional and global quality of life scale represented a better level of functioning. For the symptom scales and items, a higher score reflected a higher level of symptoms and decreased QOL.

Baseline QOL questionnaires were handed out at the first consultation with the radiation oncologist, usually 3 to 4 weeks after surgery, and had to be returned before the start of radiotherapy. The end-of-treatment QOL questionnaire was handed out 2 to 4 weeks after the completion of radiotherapy. After that time,

the questionnaires were sent directly to each patient's home address at 6, 12, 18, 24, 36, 48 and 60 months from the date of random assignment. Patients were considered evaluable for the QOL assessment if they had returned the baseline questionnaire and at least one of the follow-up questionnaires (ie, responders).

Statistical methods

All statistical analyses were performed using SPSS, version 14.0 (SPSS, Chicago, IL). Data on patient and tumor characteristics from the trial register enabled us to compare responders with nonresponders, using chi-square statistics or Fisher's exact test for categorical variables and t test for continuous variables ($p= 0.05$ was considered significant). These tests were also used to compare the VBT group with the EBRT group.

QOL analysis was done according to the guidelines provided by the EORTC Quality of life Group.[19] Descriptive median scores are listed in the tables. Baseline scores of both treatment groups were compared with a t test or the Armitage trend test for single items. To exclude a treatment effect on baseline scores, baseline forms completed later than the first day of radiotherapy were excluded for this comparison. To obtain estimates of the EORTC QLQ-C30, PR-25 and OV-28 subscales at each of the fixed time points, a linear mixed model was used with the patient as random effect and time (categorical), random assignment and their interaction as fixed effects. Single items were analyzed by using (ordinal) logistic regression with random effects. The difference in QOL between the two treatment groups was tested by Wald's test in the linear or ordinal logistic mixed model (p random assignment), which excluded the baseline value. The same test was applied to look for significant changes of QOL scores over time (p time), and score changes over time were compared between both treatment groups (p time by random assignment), which included the baseline value. To guard against false-positive results because of multiple testing, a two-sided p value of 0.01 was considered statistically significant.

Table 2. Patient functioning scores from EORTC QLQ-C30 and sexual functioning and symptom scores from OV-28.

		Questionnaire Timepoints							*P*-value		
		Baseline	*p**	After RT	6	12	18	24	Time	Randomization	Time by Randomization
EORTC QLQ-C30											
Global health status	EBRT	69,1	0,97	73,2	76,8	75,7	77,0	75,7	**<0.001**	0,35	0,82
	VBT	70,3		76,2	79,2	77,7	78,9	80,3			
Functional scales											
Physical functioning	EBRT	72,0	0,47	76,3	80,7	79,0	80,4	77,3	**<0.001**	0,24	0,98
	VBT	73,6		79,4	82,3	81,7	81,8	81,1			
Role functioning	EBRT	61,0	0,18	71,5	80,5	81,0	82,9	80,7	**<0.001**	0,29	0,66
	VBT	59,1		77,5	83,6	82,9	84,4	82,9			
Emotional functioning	EBRT	75,6	0,54	82,4	84,0	83,4	85,4	86,1	**<0.001**	0,73	0,81
	VBT	76,2		83,2	85,0	85,0	87,9	87,1			
Cognitive functioning	EBRT	84,3	0,46	86,6	86,3	86,9	87,3	85,9	0,22	0,21	0,76
	VBT	86,6		87,9	89,3	89,3	89,8	88,6			
Social functioning	EBRT	77,7	0,72	82,5	87,0	87,1	90,4	89,9	**<0.001**	**0,002**	0,42
	VBT	78,0		89,3	92,7	93,4	93,8	92,1			
EORTC OV-28											
Sexual functioning											
43. Sexual interest	EBRT	9,6	0,14	12,0	15,5	16,3	16,7	16,4	**<0.001**	0,63	0,50
	VBT	6,2		11,7	16,2	15,5	15,0	13,0			
44. Sexual activity	EBRT	6,8	0,34	11,2	14,1	14,9	13,0	13,5	**<0.001**	0,35	0,42
	VBT	3,9		8,8	13,9	12,2	13,0	10,6			
Sexual symptoms											
45. To what extent was sex enjoyable	EBRT	52,9	0,05	46,4	48,5	51,0	53,1	53,7	0,053	0,05	0,54
	VBT	23,3		50,0	47,2	42,5	50,0	42,6			
46. Vaginal dryness	EBRT	26,7	0,20	30,3	31,2	35,5	40,5	37,0	0,725	0,13	0,02
	VBT	44,4		31,6	38,9	35,6	24,4	29,6			

NOTE: for functioning scales a higher score indicates higher functioning, for symptom scales a higher score indicates more symptoms.

EORTC: European Organisation of Research and Treatment of Cancer, QLQ-C30: Core Questionnaire, OV-28: ovarian cancer module.

EBRT: external beam radiotherapy, VBT: vaginal brachytherapy, After RT: after radiotherapy

* p-value for baseline comparison, *t* test for comparing means, Armitage trend test for single items.

Results

Study population and compliance

The PORTEC-2 trial accrued 427 patients between 2002 and 2006; 214 patients were allocated to EBRT and 213 were allocated to VBT. The median follow-up at the time of analysis (January 2008) for all randomly assigned patients was 2.7 years (range, 0.9 to 5.3 years). Baseline questionnaires and at least one follow-up questionnaire were received from 348 patients (81%), who were considered responders. The median follow-up of responders was 2.7 years; because of ongoing follow-up at the time of analysis, the rate of responders at the 2-year time point was 53% (Appendix 1).

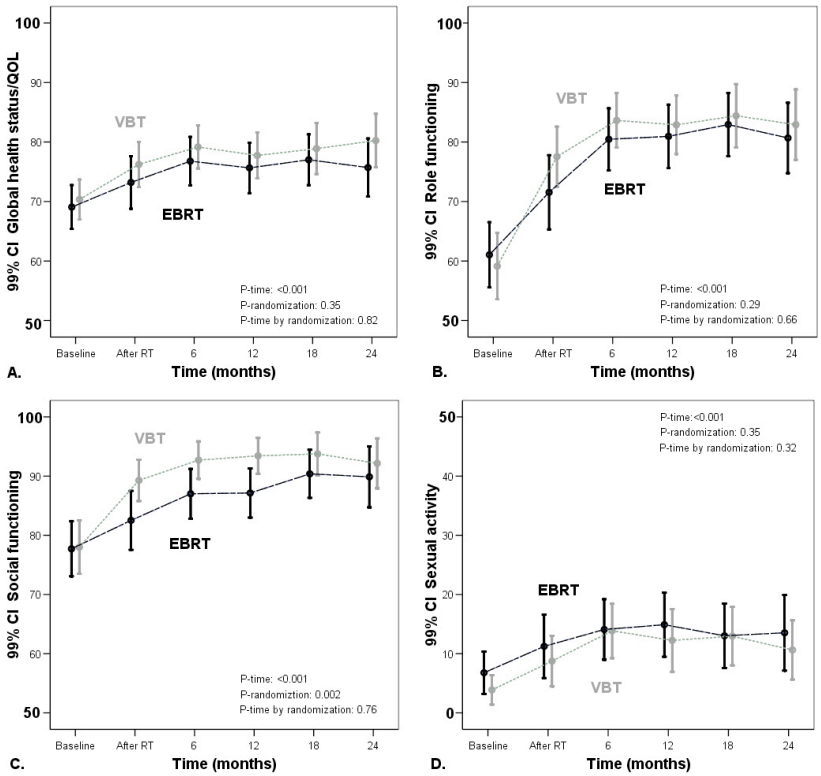
All returned questionnaires were complete for all items of the QLQ-C30 in 83% of the responders and for items on bladder and bowel symptom subscales (PR-25) in 92%. When up to two missing items were allowed, these rates were 96% and 97%, respectively. In contrast, patients were more reluctant about responding to questions about their sexual functioning and symptoms. The sexual functioning subscale (OV-28) was complete for all items in 66%; the sexual symptom subscale was complete for all items in 80% among responders who were sexually active. Overall, the treatment groups did not differ significantly with regard to questionnaire response rates and missing items. Although there were more patients who received EBRT among the nonresponders (48 patients in EBRT vs. 31 patients in VBT; p=0.04), patient characteristics were equally balanced between the EBRT and VBT groups and between responders and nonresponders (Table 1).

Table 3. Symptom scores of EORTC QLQ-C30 and PR-25.

		Questionnaire Timepoints							*P*-value		
		Baseline	*p**	After RT	6	12	18	24	Time	Randomization	Time by Randomization
EORTC QLQ-C30											
Symptom scales											
Fatigue	EBRT	34,8	0,83	32,3	24,6	25,5	23,9	24,7	**<0,001**	0,06	0,84
	VBT	34,1		26,3	21,1	20,1	19,9	18,9			
Nausea and v	EBRT	4,6	0,60	6,4	2,9	4,5	2,5	3,4	**0,001**	0,013	0,54
	VBT	5,1		3,8	2,3	1,4	2,3	1,8			
Pain	EBRT	18,4	0,25	15,7	12,9	14,4	13,2	12,6	**<0,001**	0,23	0,74
	VBT	19,5		13,6	10,5	11,7	8,9	10,6			
Dyspnoea	EBRT	13,1	0,54	14,9	11,9	20,9	13,1	11,8	0,13	0,35	**0,008**
	VBT	11,7		10,1	12,4	22,2	15,2	18,1			
Insomnia	EBRT	27,5	0,59	22,9	21,4	26,4	22,3	21,4	**0,006**	0,77	0,94
	VBT	25,7		21,0	19,3	23,6	20,4	20,7			
Appetite loss	EBRT	13,7	0,24	15,7	8,7	20,5	5,1	6,9	**<0,001**	0,10	0,02
	VBT	10,7		7,2	3,2	11,0	4,6	5,5			
Constipation	EBRT	13,7	0,74	8,2	6,5	15,1	6,6	9,0	**<0,001**	0,92	0,76
	VBT	12,8		6,5	5,4	18,0	7,1	7,5			
Diarrhea	EBRT	7,9	0,10	30,6	17,4	25,9	13,1	12,8	**<0,001**	**<0,001**	0,08
	VBT	5,0		9,1	5,4	17,5	5,2	5,6			
Financial diffic	EBRT	2,2	0,02	5,1	3,5	9,2	3,0	2,2	0,025	0,70	0,82
	VBT	5,5		4,9	3,7	9,8	3,0	2,5			
EORTC PR-25											
Urinary symptoms											
31. Frequency	EBRT	32,9	0,11	40,0	29,4	32,6	30,6	30,2	**<0,001**	0,09	0,32
	VBT	36,6		36,9	29,6	24,0	26,7	29,4			
32. Frequency	EBRT	31,2	0,11	38,3	28,7	29,5	29,8	29,5	**<0,001**	0,19	0,17
	VBT	34,3		34,3	27,0	25,2	30,6	31,6			
33. Urinary ur	EBRT	22,4	0,33	39,4	26,3	31,9	32,3	34,3	**0,005**	0,015	0,02
	VBT	23,3		24,6	28,0	27,3	30,2	28,3			
34. Sleep	EBRT	14,4	0,07	20,0	13,1	16,7	13,4	13,2	**0,009**	0,05	0,10
deprivation	VBT	16,3		13,8	10,9	13,9	13,2	15,4			
35. Need to	EBRT	7,3	0,39	21,4	14,2	15,0	13,3	12,9	0,02	**<0,001**	0,42
remain close	VBT	7,1		8,7	7,0	7,3	8,4	7,9			
36.	EBRT	11,0	0,95	18,1	12,3	16,8	15,7	16,2	0,016	0,40	0,35
Incontinence	VBT	10,6		13,0	14,0	15,4	14,8	16,0			
37. Dysuria	EBRT	5,3	0,37	8,6	3,2	2,9	1,4	2,5	**<0,001**	0,61	0,80
	VBT	8,0		9,4	3,6	3,3	1,2	1,1			
38. Limitation	EBRT	3,4	0,54	8,6	5,2	7,0	5,1	8,3	**0,005**	0,85	0,88
daily	VBT	3,1		5,4	4,4	3,8	4,9	6,2			
Bowel symptoms											
39. Limitation	EBRT	8,9	0,08	21,8	15,2	14,5	13,8	13,7	**<0,001**	**<0,001**	0,48
daily	VBT	5,2		6,3	5,0	3,6	4,6	2,8			
40. Fecal	EBRT	4,0	0,26	9,3	10,5	7,8	8,4	8,7	**0,002**	**<0,001**	0,12
leakage	VBT	1,5		3,8	2,3	2,2	3,6	1,7			
41. Rectal blo	EBRT	0,4	0,95	2,2	2,1	1,0	2,5	1,6	0,162	0,04	0,57
	VBT	0,2		1,2	0,8	0,9	0,2	0,8			
42. Bloated fe	EBRT	16,1	0,61	16,8	15,4	14,4	12,6	10,8	**0,006**	0,15	0,96
	VBT	15,5		14,2	12,4	9,6	9,6	8,8			

NOTE: for functioning scales a higher score indicates higher functioning, for symptom scales a higher score indicates more symptoms.
EORTC: European Organisation of Research and Treatment of Cancer, QLQ-C30: Core Questionnaire, PR-25: prostate cancer module.
US: urinary symptoms, BS: bowel symptoms, EBRT: external beam radiotherapy, VBT: vaginal brachytherapy after RT: after radiotherapy
* p-value for baseline comparison, t test for comparing means, Armitage trend test for single items.

Figure 1. Patient functioning, subscales from EORTC QLQ-C30 and OV-28



Note: for functioning scales a higher score indicates a higher level of functioning. Bars represent 99% confidence intervals. For figures A, B and C the vertical axis is in the upper 50% range, for figure D in the lower 50% range.

Patient functioning

Mean scores of the EORTC QLQ-C30 functioning subscales and global health status, and for the OV-28 subscales on sexual functioning and symptoms are summarized in Table 2. Development of the functioning scores over time is displayed in Figure 1. Baseline functioning scores did not differ significantly between the treatment groups. For both treatment groups, global heath status and functioning scales were low at baseline, showed a significant improvement in the first 6 months, and reached a plateau at 12 months (Fig 1).

Patients treated with VBT reported significantly higher social functioning scores after radiotherapy and with additional follow-up than patients treated with EBRT. The maximum difference between both treatment groups was 6%

after radiotherapy (EBRT 83% vs. VBT 89%, p random assignment = 0.002); this difference remained at approximately the same level during the first year of follow-up. Mean scores for global health status and for the remaining functioning scores were somewhat higher for patients treated with VBT, but these differences were not statistically significant.

Sexual activity and interest were lowest at baseline (ie, after surgery), when 15% of the patients indicated that they were sexually active. Both interest and activity increased significantly during the first 6 months to reach a plateau (39% active), without significant differences between the treatment groups. Of the patients who indicated they were active, 80% reported on their sexual symptoms; in these patients there were no significant differences in sexual symptoms.

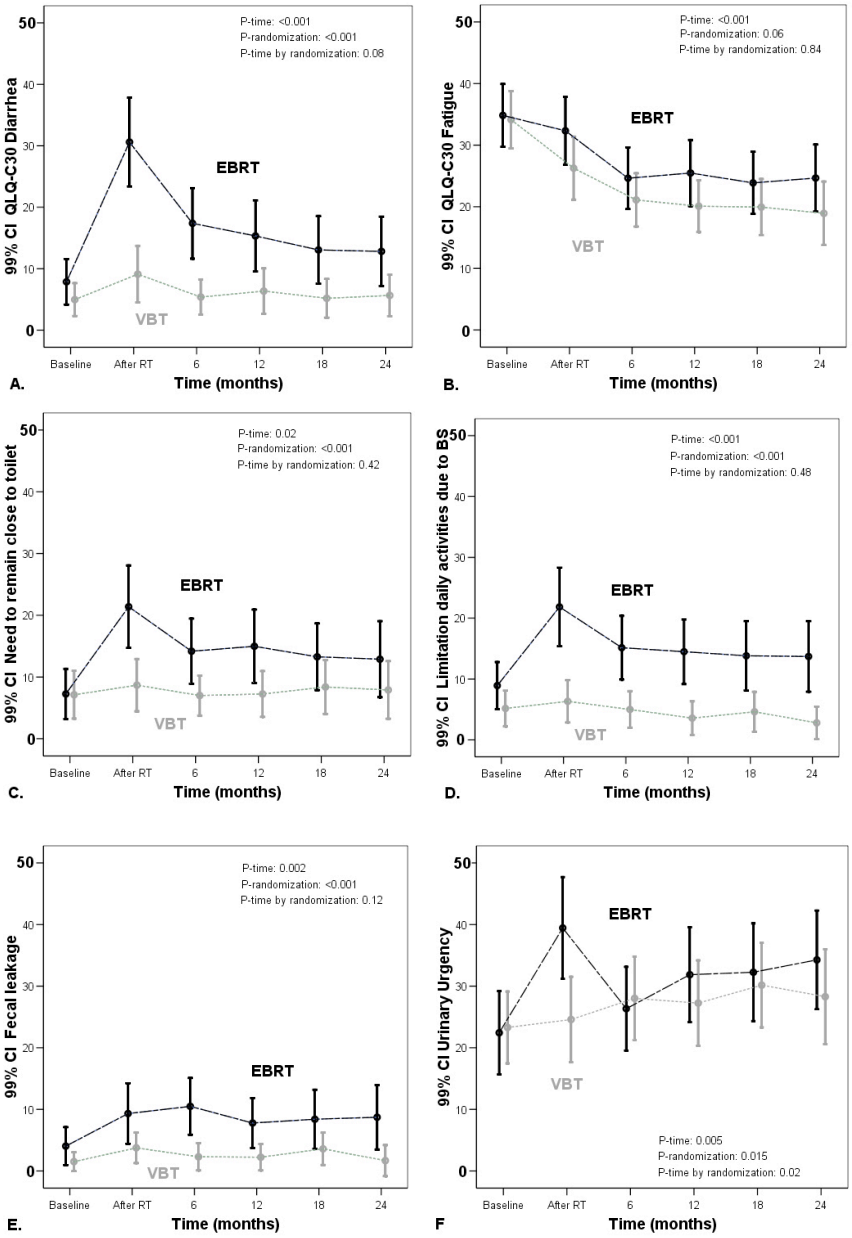
Symptom scores

Mean scores on the symptom scales of EORTC QLQ-C30, PR-25 and OV-28 are summarized in Table 3. Development of the mean symptom scores over time is displayed in Figure 2, and development of patient responses is in Figure 3. Baseline symptom scores did not differ significantly between the treatment groups. Patients treated with EBRT reported a 21% increase in mean diarrhea scores after radiotherapy, as compared to patients treated with VBT (30% EBRT vs. 9% VBT, p random assignment <0.001). After EBRT, 15.4% and 7.3% of the patients reported “quite a bit” or “very much” diarrhea, respectively, whereas these rates were 2.8% and 2.8%, respectively after VBT (Fig 3). Although diarrhea scores of the patients in the EBRT group decreased, they remained at significantly higher levels with additional follow-up. Conversely, diarrhea scores in the VBT group remained low, at baseline level (p time < 0.001).

In addition, patients treated with EBRT reported an 8% increase in mean scores of fecal leakage 6 months after radiotherapy (10% EBRT vs. 2% VBT, p random assignment <0.001), and scores remained stable with additional follow-up. Within the bowel symptom subscale the item on ‘limitations of daily activities due to bowel problems’ showed the largest difference (15%) between the treatment groups, in favor of VBT (22% EBRT vs. 6% VBT, p random assignment <0.001). Although there was a trend toward a higher level of urinary urgency after EBRT (p random assignment = 0.015), the same question on limitation of daily

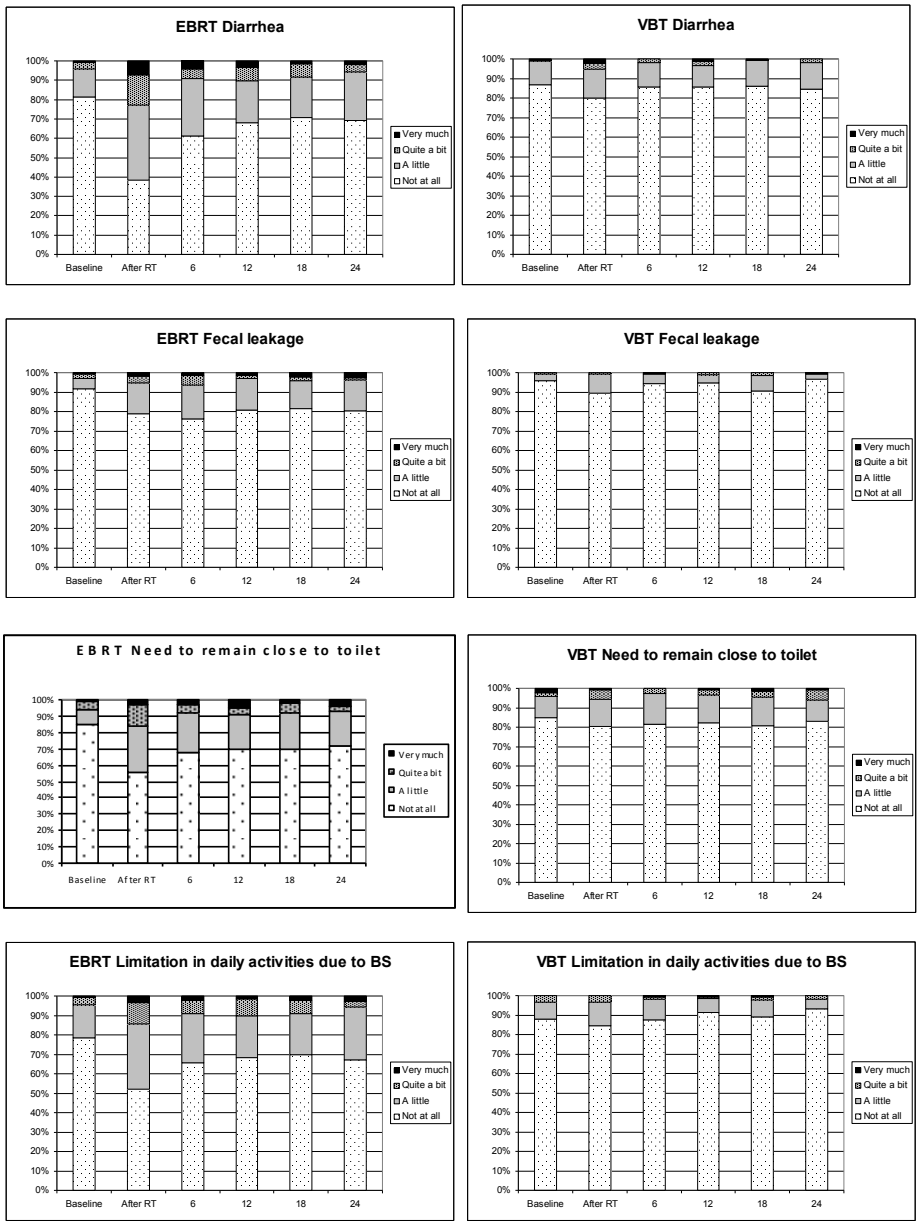
activities because of bladder problems did not show a significant difference. In fact, the only urinary symptom item that showed a significant difference between treatment groups, both after radiotherapy and with additional follow-up, was the question, "Have you had difficulty going out of the house because you needed to be close to a toilet?" This question is however not specific for urinary symptoms, and could also be related to bowel symptoms. Two general patterns of change in symptom scores over time could be distinguished (Fig 2). In the first pattern baseline symptom scores were high, and decreased in the subsequent time points to reach a plateau around 12 months. Fatigue, nausea and vomiting, pain, appetite loss, and constipation are examples of this first pattern and are considered symptoms related to recovery from surgery. The second pattern is associated with RT, as baseline scores are low, but increase significantly during and after radiotherapy before declining again (eg, bowel and urinary symptoms).

Figure 2. Summary scores for symptom scales of EORTC QLQ-C30 and PR-25.



Note: for symptom scales a higher score indicates more symptoms. Bars represent 99% confidence intervals. For all figures the vertical axis is in the lower 50% range. Scores correspond to summary scores presented in Table 3. BS: bowel symptoms.

Figure 3. Patient responses on single item symptom scales of: diarrhea, fecal leakage, need to remain close to the toilet and limitation in daily activities due to bowel symptoms.



Discussion

To our knowledge, PORTEC-2 is the first phase III, randomized, multicenter trial to compare the efficacy of VBT and EBRT, to determine which treatment provides optimal local control with least morbidity and best QOL for patients with high-intermediate risk endometrial cancer. In this first analysis of patient-reported QOL during the first two years after treatment, marked differences between the treatment groups were found.

Bowel symptoms such as diarrhea and fecal leakage were significantly increased after EBRT compared with VBT. Furthermore, patients treated with EBRT reported a significantly higher need to remain close to a toilet, which resulted in a higher level of limitation of daily activities because of bowel problems. Finally, social functioning after EBRT was at a significant lower level than after VBT. These differences remained stable with additional follow-up.

Although higher fatigue rates among the patients who underwent EBRT were expected[13], a sharp decrease of fatigue rates during radiotherapy and during the first year after treatment in both groups was observed. The trend was towards less fatigue after VBT compared with EBRT (p=0.06).

Reported late side effects of vaginal brachytherapy include vaginal dryness with painful intercourse and tightening and/or shortening of the vagina.[20-23] Little is known about the influence of these adverse effects on sexual functioning. Patients generally were more reluctant to respond to questions on this subject; 66% completed the questions on sexual activity. Nonetheless, 39% of these elderly women indicated they were sexually active at 6 months after surgery, which is in the range of results reported in elderly women.[24] Other than the significant increase in sexual activity in both treatment groups, there were no significant differences in sexual functioning or symptoms between the groups.

The observed increases in diarrhea scores (on QLQ-C30) and bowel symptoms (on PR-25) show the internal consistency of these main findings. The same is true for the lower levels of social functioning and increased limitation of daily activities reported by patients treated with EBRT. Increased bowel symptoms and diarrhea scores after EBRT are consistent both with clinical experience and the higher rates of gastro-intestinal toxicity reported in the randomized trials.[4,6]

In the PORTEC-1 trial the rate of grade 1-4 late toxicity for EBRT patients was

26%, of which 20% was gastro-intestinal toxicity (grades 1 to 2, 17%; grades 3 to 4, 3%).4 Phase II studies of VBT reported very low rates of gastro-intestinal toxicity, consistent with the finding that symptom scores among the PORTEC-2 VBT arm remained at baseline level.[20-23]

Reference values of the Swedish and Danish norm-population for the EORTC QLQ-C30 show higher functioning scores and lower symptom rates as compared to the baseline scores for both EBRT and VBT groups.[25,26] However, the plateau that occurred in most scores 6 to 12 months after treatment is in the range of these reference values, which indicates that, for most women, the stressful period of diagnosis and treatment for endometrial cancer has a clear but transient influence on their functioning. This observation is in concordance with the largest retrospective HRQOL study among patients with endometrial cancer at 5 to 10 years after treatment; in this study, scores of patients treated with and without EBRT were similar to those of an age matched population, although scores on vitality and physical and social well-being were significantly lower when EBRT patients were compared to patients who had received no radiotherapy.[13]

When changes in QOL scores are interpreted, definition of a clinically relevant change in a score is important. Earlier studies on the magnitude of clinically relevant differences agree on a difference of 5% to 10% of the instrument range as being clinically relevant.[27-29] For the EORTC Core questionnaire, Osoba et al[28] found that patients valued a change of 5-10% as little, 10-20% as moderate and more than 20% as very much difference. For these results, this would mean that there was very much improvement in functioning scales in the first 6 months after surgery for both groups. Furthermore, patients treated with EBRT reported very much diarrhea and little symptoms of fecal leakage, while patients treated with VBT did not report an increase in these symptoms. In addition, patients treated with EBRT reported a moderate increase in the need to remain close the toilet because of bowel symptoms and limitation of daily activities. This resulted in little reduction of social functioning for EBRT patients.

In conclusion, patients who received external beam radiotherapy reported significant and clinically relevant higher levels of diarrhea and fecal leakage. This resulted in a higher need to remain close to a toilet, more limitation of daily activities because of bowel symptoms, and decreased social functioning. VBT did not have this negative effect on HRQOL and can be regarded the preferred treatment from a HRQOL perspective. This QOL benefit will have to be balanced against the outcome of the efficacy analysis. First results suggest that VBT is effective and should be regarded as the treatment of choice for patients with high-intermediate risk endometrial carcinoma.[30]

References

1. Bray F, Loos AH, Oostindier M, Weiderpass E. Geographic and temporal variations in cancer of the corpus uteri: incidence and mortality in pre- and postmenopausal women in Europe. Int J Cancer 117:123-131, 2005
2. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 56:419-427, 1980
3. Creutzberg CL, van Putten WL, Koper PC et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 355:1404-1411, 2000
4. Creutzberg CL, van Putten WL, Koper PC et al. The morbidity of treatment for patients with Stage I endometrial cancer: results from a randomized trial. Int J Radiat Oncol Biol Phys 51:1246-1255, 2001
5. J.Orton, P.Blake, on behalf of ASTEC/EN.5 collaborators. Adjuvant external beam radiotherapy (EBRT) in the treatment of endometrial cancer: Results of the randomised MRC ASTEC and NCIC CTG EN.5 trial. J.Clin.Oncol. 25[18S]. 20-6-2007. Ref Type: Abstract
6. Keys HM, Roberts JA, Brunetto VL et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 92:744-751, 2004
7. Scholten AN, van Putten WL, Beerman H et al. Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys 63:834-838, 2005
8. Bradley S, Rose S, Lutgendorf S, Costanzo E, Anderson B. Quality of life and mental health in cervical and endometrial cancer survivors. Gynecol Oncol 100:479-486, 2006
9. Bye A, Trope C, Loge JH, Hjermstad M, Kaasa S. Health-related quality of life and occurrence of intestinal side effects after pelvic radiotherapy--evaluation of long-term effects of diagnosis and treatment. Acta Oncol 39:173-180, 2000
10. Klee M, Machin D. Health-related quality of life of patients with endometrial cancer who are disease-free following external irradiation. Acta Oncol 40:816-824, 2001
11. Li C, Samsioe G, Iosif C. Quality of life in endometrial cancer survivors. Maturitas 31:227-236, 1999
12. Zhu L, Le T, Popkin D, Olatunbosun O. Quality-of-life analysis in the management of endometrial cancer. Am J Obstet Gynecol 192:1388-1390, 2005
13. van de Poll-Franse LV, Mols F, Essink-Bot ML et al. Impact of External Beam Adjuvant Radiotherapy on Health-Related Quality of Life for Long-Term Survivors of Endometrial Adenocarcinoma: A Population-Based Study. Int J Radiat Oncol Biol Phys , 2007

14. Shepherd JH. Revised FIGO staging for gynaecological cancer. Br J Obstet Gynaecol 96:889-892, 1989
15. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 26:2389-2430, 2007
16. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365-376, 1993
17. Aaronson NK, van Andel G., EORTC Genito Urinary TractCancer Group. An international field of the reliability and validity of the QLQ-C30 and a disease-specific questionnaire module (QLQ-PR25) for assessing quality of life of patients with prostate cancer. European Organization for Research and Treatment of Cancer study protocol (15011). Brussels: 2002.
18. Greimel E, Bottomley A, Cull A et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur J Cancer 39:1402-1408, 2003
19. Fayers PM, Aaronson NK, Bjordal K, Curran D, Groenvold M, on behalf of the EORTC Quality of Life Study Group. EORTC QLQ-C30 Scoring Manual (Second edition). Brussels: EORTC; 1999.
20. Chadha M, Nanavati PJ, Liu P, Fanning J, Jacobs A. Patterns of failure in endometrial carcinoma stage IB grade 3 and IC patients treated with postoperative vaginal vault brachytherapy. Gynecol Oncol 75:103-107, 1999
21. Eltabbakh GH, Piver MS, Hempling RE, Shin KH. Excellent long-term survival and absence of vaginal recurrences in 332 patients with low-risk stage I endometrial adenocarcinoma treated with hysterectomy and vaginal brachytherapy without formal staging lymph node sampling: report of a prospective trial. Int J Radiat Oncol Biol Phys 38:373-380, 1997
22. Pearcey RG, Petereit DG. Post-operative high dose rate brachytherapy in patients with low to intermediate risk endometrial cancer. Radiother Oncol 56:17-22, 2000
23. Weiss E, Hirnle P, Arnold-Bofinger H, Hess CF, Bamberg M. Adjuvant vaginal high-dose-rate afterloading alone in endometrial carcinoma: patterns of relapse and side effects following low-dose therapy. Gynecol Oncol 71:72-76, 1998
24. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med 357:762-774, 2007
25. Klee M, Groenvold M, Machin D. Quality of life of Danish women: population-based norms of the EORTC QLQ-C30. Qual Life Res 6:27-34, 1997
26. Michelson H, Bolund C, Nilsson B, Brandberg Y. Health-related quality of life measured by the EORTC QLQ-C30--reference values from a large sample of Swedish population. Acta Oncol 39:477-484, 2000
27. Barrett B, Brown D, Mundt M, Brown R. Sufficiently important difference: expanding the framework of clinical significance. Med Decis Making 25:250-261, 2005

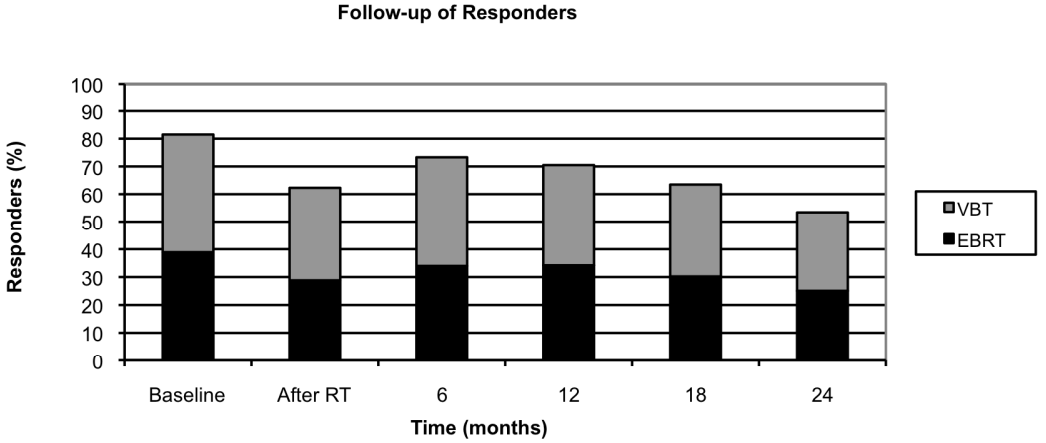
28. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 16:139-144, 1998
29. Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. Cancer 110:196-202, 2007
30. Nout RA, Putter H, Jürgenliemk-Schulz IM et al. Vaginal brachytherapy versus external beam pelvic radiotherapy for high-intermediate risk endometrial cancer: results of the randomized PORTEC-2 trial. LBA5503. J.Clin.Oncol. 26[18S], 1010s. 2008. Ref Type: Abstract

Appendix 1.

Web appendix Table: Follow-up of Responders

	Baseline		After RT		6 months		12 months		18 months		24 months	
	No. of responders	%	No. of responders	%	No. of responders	%	No. of responders	%	No. of responders	%	No. of responders	%
EBRT	166	48,3	123	46,2	145	46,3	146	48,5	129	47,6	107	46,9
VBT	182	52,9	143	53,8	168	53,7	155	51,5	142	52,4	121	53,1
Total Responders	344		266		313		301		271		228	
Responders as % of total randomized (N=427)	80,6		62,3		73,3		70,5		63,5		53,4	

EBRT: External Beam Radiotherapy; VBT: Vaginal Brachytherapy
Responders: patients who handed in the baseline questionnaire and at least one follow-up questionnaires.
NOTE: Due to ongoing follow-up at time of analysis, the rate of responders gradualy decreased to 53% at 24 months.



3

Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial

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Summary

Background: After surgery for intermediate-risk endometrial carcinoma (EC), the vagina is the most frequent site of recurrence. This study established whether vaginal brachytherapy (VBT) is as effective as pelvic external beam radiotherapy (EBRT) in prevention of vaginal recurrence, with fewer adverse effects and improved quality of life.

Methods: In this open-label, non-inferiority, randomised trial undertaken in 19 Dutch radiation oncology centres, 427 patients with stage I or IIA endometrial cancer with features of high-intermediate risk were randomly assigned by a computer-generated, biased coin minimisation procedure to pelvic EBRT (46 Gy in 23 fractions; n=214) or VBT (21 Gy high-dose rate in 3 fractions, or 30 Gy low-dose rate; n=213). All investigators were masked to the assignment of treatment group. The primary endpoint was vaginal recurrence. The predefined non-inferiority margin was an absolute difference of 6% in vaginal recurrence. Analysis was by intention to treat, with competing risk method. The study is registered, number ISRCTN16228756.

Findings: At median follow-up of 45 months (range 18-78), three vaginal recurrences had been diagnosed after VBT and four after EBRT. Estimated 5-year rates of vaginal recurrence were 1.8% (95% CI 0.6 - 5.9) for VBT and 1.6% (0.5 – 4.9) for EBRT (hazard ratio [HR] 0.78, 95% CI 0.17 – 3.49; p=0.74). Five-year rates of locoregional relapse (vaginal or pelvic recurrence, or both) were 5.1% (2.8 – 9.6) for VBT and 2.1% (0.8 – 5.8) for EBRT (HR2.08, 0.71 – 6.09; p=0.17). 1.5% (0.5 – 4.5) vs 0.5% (0.1 – 3.4) of patients presented with isolated pelvic recurrence (HR 3.10, 0.32 – 29.9; p=0.30), and rates of distant metastasis were similar (8.3% [5.1 – 13.4] vs 5.7% [3.3 – 9.9]; HR 1.32, 0.63 – 2.74; p=0.46). We recorded no differences in overall (84.8% [95% CI 79.3 – 90.3] vs 79.6% [71.2 – 88.0]; HR 1.17, 0.69 – 1.98; p=0.57) or disease-free survival (82.7% [76.9 – 88.6] vs 78.1% [69.7 – 86.5]; HR 1.09, 0.66 – 1.78; p=0.74). Rates of acute grade 1-2 gastrointestinal toxicity were significantly lower in the VBT group than in the EBRT group at completion of radiotherapy (12.6% [27/215] vs 53.8% [112/208]).

Interpretation: VBT is effective in ensuring vaginal control, with fewer gastrointestinal toxic effects than with EBRT. VBT should be the adjuvant treatment of choice for patients with endometrial carcinoma of high-intermediate risk.

Introduction

Endometrial carcinoma is the most common gynaecological malignant disease in postmenopausal women in developed countries.[1] About 80% of patients present with early stage disease (International Federation of Gynecology and Obstetrics [FIGO] stage I, limited to the uterine corpus) and have a favourable prognosis. Surgery consisting of total abdominal hysterectomy and bilateral salpingo-oophorectomy is the basis of treatment.

Both the first Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC-1) trial and the Gynecological Oncology Group (GOG) 99 trial compared pelvic external beam radiotherapy (EBRT) with no additional treatment for patients with stage I endometrial carcinoma, and showed that EBRT significantly reduced the rate of locoregional (vaginal or pelvic, or both) recurrence.[2-4] Both trials defined a so-called group of high-intermediate risk that showed the largest absolute reduction of locoregional recurrence after EBRT. In PORTEC-1, major risk factors for recurrence were invasion in the outer half of the myometrium, grade 3 histology, and age greater than 60 years.[2, 4] For patients at high-intermediate risk with two of these three major risk factors, locoregional at 5 years was reduced from 23% to 5% after EBRT.[2, 4] In GOG 99, EBRT provided a 58% hazard reduction of 4-year cumulative recurrence in the group at high-intermediate risk (from 27% to 13%), and reduction of isolated initial local recurrence from 13% to 5%.[3] In both trials this reduction was mainly caused by reduction of vaginal recurrence, which accounted for 75% of locoregional recurrence in the group receiving no additional treatment. EBRT did not improve overall survival, and rates of distant metastases were similar. In PORTEC-1, adverse effects were recorded in 26% of patients receiving EBRT, predominantly mild gastrointestinal toxic effects.[5]

Retrospective studies reported vaginal brachytherapy (VBT) to be very effective in prevention of vaginal recurrence.[6-10] The randomised PORTEC-2 trial was started to investigate whether VBT would be equally effective as EBRT in reduction of vaginal recurrence, with fewer treatment-related toxic effects and improved quality of life. Analysis of quality of life reported by patients in PORTEC-2 during the first two years after treatment has shown that

those who had received EBRT reported significantly more, clinically relevant gastrointestinal symptoms, especially diarrhoea,[11] resulting in restriction of daily activities and decreased social functioning.

This study aimed to compare outcomes and adverse effects after VBT and EBRT, and to establish optimum adjuvant treatment for patients with endometrial carcinoma of high-intermediate risk.

Methods

Patient selection and eligibility criteria

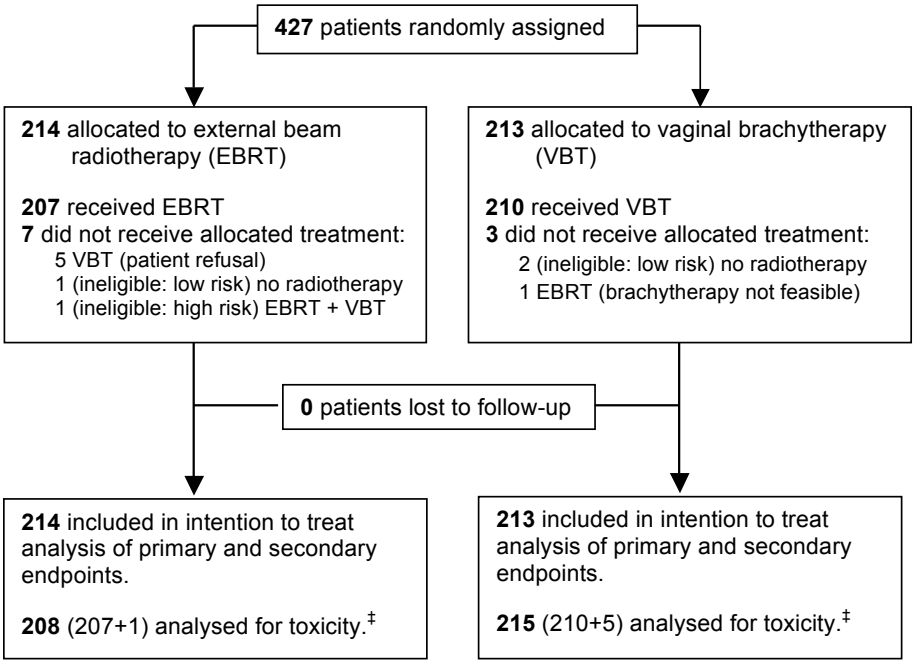
The PORTEC-2 trial was a multicenter randomised trial, in which 19 of the 21 Dutch radiation oncology centres participated. The study was undertaken between May 27, 2002 and Sept 25, 2006. Patients were assessed and operated on by their regional gynaecologist. Initial assessment included pelvic examination, and endometrial tissue biopsy. Preoperative evaluation included chest radiography and haematology and chemistry tests. During surgery a peritoneal cytology specimen was obtained and abdominal exploration undertaken. Surgery consisted of total abdominal hysterectomy and bilateral salpingo-oophorectomy; clinically suspicious pelvic or periaortic lymph nodes were removed, but no routine lymphadenectomy was done. Diagnosis, typing and grading of endometrial carcinoma was done by the regional pathologist. FIGO 1988 staging was assigned on the basis of surgical and pathological findings.[12]

Patients with endometrial adenocarcinoma were eligible for the trial on the basis on the following features of high-intermediate risk: (1) Age greater than 60 years and stage 1C grade 1 or 2 disease, or stage 1B grade 3 disease; and (2) stage 2A disease, any age (apart from grade 3 with greater than 50% myometrial invasion). All patients had a WHO-performance score of 0-2. Exclusion criteria were: serous or clear cell carcinoma; staging lymphadenectomy; interval between surgery and radiotherapy more than 8 weeks; history of previous malignant disease; previous radiotherapy, hormonal therapy or chemotherapy; and previous diagnosis of Crohn's disease or ulcerative colitis. We obtained written informed consent from all patients. The protocol was approved by the Dutch Cancer Society and the Ethics Committees of all participating centres.

Randomisation and masking

Participants were assigned to either EBRT or VBT via internet with an application trial on line process (TOP). Patient details and answers about eligibility questions were entered by the data managers of the participating centres, after which treatment was allocated by TOP with a biased coin minimisation procedure, with stratification factors FIGO stage, radiotherapy centre, brachytherapy (low-dose vs. high-dose rate), and patient age (<60 years vs. ≥60 years). The outcome of the allocation was computer generated and not predictable by the investigators. Once the trial group was assigned, the treatment and the assessment of the outcomes were unmasked.

Figure 1. Trial profile
EBRT= external beam radiotherapy. VBT= vaginal brachytherapy. ‡ Toxicity analysis was performed for treatment received. We did not record data for the total number of patients diagnosed and who received primary treatment in the participating centres.



Procedures

The primary endpoint was vaginal recurrence. Secondary endpoints were locoregional recurrence (vagina or pelvic, or both), distant metastases, overall and disease-free survival, treatment-related toxic effects, and quality of life (reported elswhere11).

The clinical target volume for EBRT consisted of the proximal half of the vagina, the parametrial tissues, the internal and proximal external iliac lymph node region, and the caudal part of the common iliac lymph node chain (up to 1 cm below the level of the promontory). The planning target volume consisted of the clinical target volume with a 1 cm three-dimensional margin.

A dose of 46 Gy, with 2 Gy fractions, five times per week, was prescribed to the planning target volume and specified at the isocenter, with homogeneity requirements according to recommendations of the International Commission of Radiation Units and Measurements (ICRU-50). For all patients computerized treatment planning was done using three-dimensional conformal or multiple field techniques, with individual shielding in all fields. Centres had to complete a dummy-run procedure prior to activation the trial.

Brachytherapy was delivered with a vaginal cylinder, with the reference isodose covering the proximal half of the vagina. The dose was specified at 5 mm distance from the surface of the cylinder. The dose at 5 mm cranially from the vaginal vault along the axis of the cylinder could not vary more than plus or minus 10% of the specified dose. Dose schedules with a low-dose and high-dose rate were prescribed, with a dose equivalent to 45-50 Gy to the vaginal mucosa: 21 Gy in three fractions of 7 Gy, 1 week apart for the high-dose rate; 30 Gy at 50-70 cGy/hr for the low-dose rate; and 28 Gy at 100 cGy/hr in one session for the medium-dose rate. Centres had to use the same treatment schedule throughout the trial. Doses in the bladder and rectum reference points (according to ICRU-38 criteria) and at the vaginal mucosal surface were documented.

Patients were assessed by their radiation oncologist 2-4 weeks after completion of radiotherapy. Alternating follow-up visits to the gynaecologist and radiation oncologist were planned every 3 months in the first 2 years, every 6 months until year 5, and then every year, up to ten years. Pelvic examination was

Table 1. Patient and tumour characteristics.

	EBRT (N=214)		**VBT** (N=213)	
	No. of patients	%	No. of patients	%
Median age ± SD, yrs	69 ± 7		70 ± 7	
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
KPS				
0	157	73.4	141	66.5
1	56	26.2	66	31.1
2	1	0.5	5	2.4
Co-morbidity				
IBD	4	1.9	2	0.9
Diabetes	28	13.1	34	16.0
Hypertension	75	35.0	75	35.2
Cardiovascular	47	22.0	51	24.0
Other	33	15.4	33	15.5
FIGO stage				
IB	19	8.9	16	7.5
IC	172	80.4	171	80.3
IIA	23	10.7	26	12.2
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	191	90.1
Distance to serosa				
0-1 mm.	17	14.2	23	16.9
2-3 mm.	46	38.3	43	31.6
4-5 mm.	35	29.2	36	26.5
≥ 6 mm.	22	18.3	34	25
not recorded	94	43.9	77	36.2
median mm. (± SD))	3.8 (±2.5)		4.3 (±3.2)	
Interval surgery-radiotherapy, days (SE)	43.4 (0.8)		42.5 (0.8)	
Duration of radiotherapy, days (SE)	30.9 (0.2)		12.9 (0.4)	
Mean dose, SE (Gy)				
EBRT	46.0 (0.9)			
VBT: HDR‡			21.1 (0.1)	
VBT: MDR‡			28.5 (0.5)	
VBT: LDR‡			29.0 (0.3)	
VBT median cylinder diameter (mm. + range)			30 (20-40)	
VBT mean length of 100% isodose (mm. + SE)			46.5 (0.7)	

EBRT: external beam radiotherapy; VBT: vaginal brachytherapy KPS: Karnofsky Performance Score; IBD: irritable bowel syndrome, LVSI: lymph vascular space invasion
‡VBT was delivered with high-dose-rate (HDR) in 182 (85.4%)patients; with low-dose-rate (LDR) in 19 (9.0%) patients; and medium-dose-rate (MDR) in 8 (3.8%) patients.

Table 2. Recurrence and survival (all patients), after a median follow-up of 45 months.

	Events/Total	Estimated 5-year % (95% CI)	Hazard Ratio (95% CI)*	Log-rank *p* value*
Vaginal Recurrence				
EBRT	4/214	1.6 (0.5 - 4.9)	1	0.74
VBT	3/213	1.8 (0.6 - 5.9)	0.78 (0.17-3.49)	
Pelvic Recurrence				
EBRT	1/214	0.5 (0.1 - 3.4)	1	0.02
VBT	8/213	3.8 (1.9 - 7.5)	8.29 (1.04-66.4)	
Locoregional Recurrence				
EBRT	5/214	2.1 (0.8 - 5.8)	1	0.17
VBT	10/213	5.1 (2.8 - 9.6)	2.08 (0.71-6.09)	
Distant Metastases				
EBRT	13/214	5.7 (3.3 - 9.9)	1	0.46
VBT	16/213	8.3 (5.1 - 13.4)	1.32 (0.63-2.74)	
First Failure Type				
Vaginal Recurrence				
EBRT	2/214	1.1 (0.3 - 4.4)	1	0.57
VBT	1/213	0.9 (0.1 - 6.2)	0.51 (0.05-5.58)	
Pelvic Recurrence				
EBRT	1/214	0.5 (0.1 - 3.4)	1	0.30
VBT	3/213	1.5 (0.5 - 4.5)	3.10 (0.32-29.9)	
Disease Free Survival				
EBRT	31/214	78.1 (69.7 - 86.5)	1	0.74
VBT	32/213	82.7 (76.9 - 88.6)	1.09 (0.66-1.78)	
Overall Survival				
EBRT	26/214	79.6 (71.2 - 88.0)	1	0.57
VBT	29/213	84.8 (79.3 - 90.3)	1.17 (0.69-1.98)	

done at every visit. We assessed acute and late side-effects with the grading system of the European Organisation of Research and Treatment of Cancer and Radiation Therapy Oncology Group (EORTC-RTOG) for radiation toxic effects.14 For assessment of late effects in the vaginal mucosa that were clinically recorded at pelvic examination, EORTC-RTOG grading for mucous membrane was used. Any atrophic changes were reported as grade 1 (minor atrophy), and moderate atrophy with or without telangiectasia as grade 2 mucosal toxic effects. Chest radiograph, blood count and chemistry tests were obtained every year. Vaginal or pelvic recurrences had to be confirmed by histology, and patients with recurrence were screened for distant metastasis.
Eligibility check and randomization were done based on the original pathology diagnosis. Central review of the pathology was done to assess histological type, stage and grade, especially as previous studies have indicated poor reproducibility of tumour grading.4, 15 At review criteria for high-intermediate risk could be confirmed, or patients could be either reclassified to high-risk (non-endometrioid type carcinoma, IC grade 3, or stage IIB or higher), or low-risk groups.

Statistical Analysis

On the basis of data from the PORTEC-1 trial, vaginal recurrence was expected to be 2% after 3 years in the EBRT group. In view of the absence of survival benefit with either EBRT and VBT and of the expected reduced risk of side effects with VBT, the aim of the trial was to estimate the difference in vaginal recurrence with sufficient precision (SE <2%) and to exclude a clinically relevant absolute difference in efficacy. An accrual of 400 patients in 4 years would provide the study with adequate power (85%) to detect a clinically relevant absolute difference of 6% in vaginal recurrence (2% vs 8%, hazard ratio [HR] 4.1) between both arms (one-sided test).

Analysis was done by intention-to-treat. Time-to-event analyses were done with log-rank tests and Cox proportional hazards regression models with date of randomization 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. Data on patients who were alive and free of recurrence were censored at date of last follow-up. The competing risks method (with death as competing risk) was used for analysis of the rates of vaginal recurrence, pelvic recurrence, locoregional recurrence and distant metastases.[13] The Kaplan-Meier method was used for overall and disease-free survival. A first failure competing risks analysis was done when the first failure type was distant if there was distant metastasis, with or without simultaneous vaginal or pelvic recurrence. The failure type was pelvic recurrence if there was pelvic recurrence with or without vaginal recurrence; the failure type was vaginal recurrence in the case of isolated vaginal recurrence. Analysis of toxicity was based on treatment received.

All statistical analyses were done with SPSS, version 16.0 (SPSS, Inc, Chicago, IL). Patient- and tumour characteristics and data for toxic effects were compared with chi-square statistics or Fisher's exact test for categorical variables, and *t* test for continuous variables (p-value < 0.05 was considered significant). The study is registered, number ISRCTN16228756.

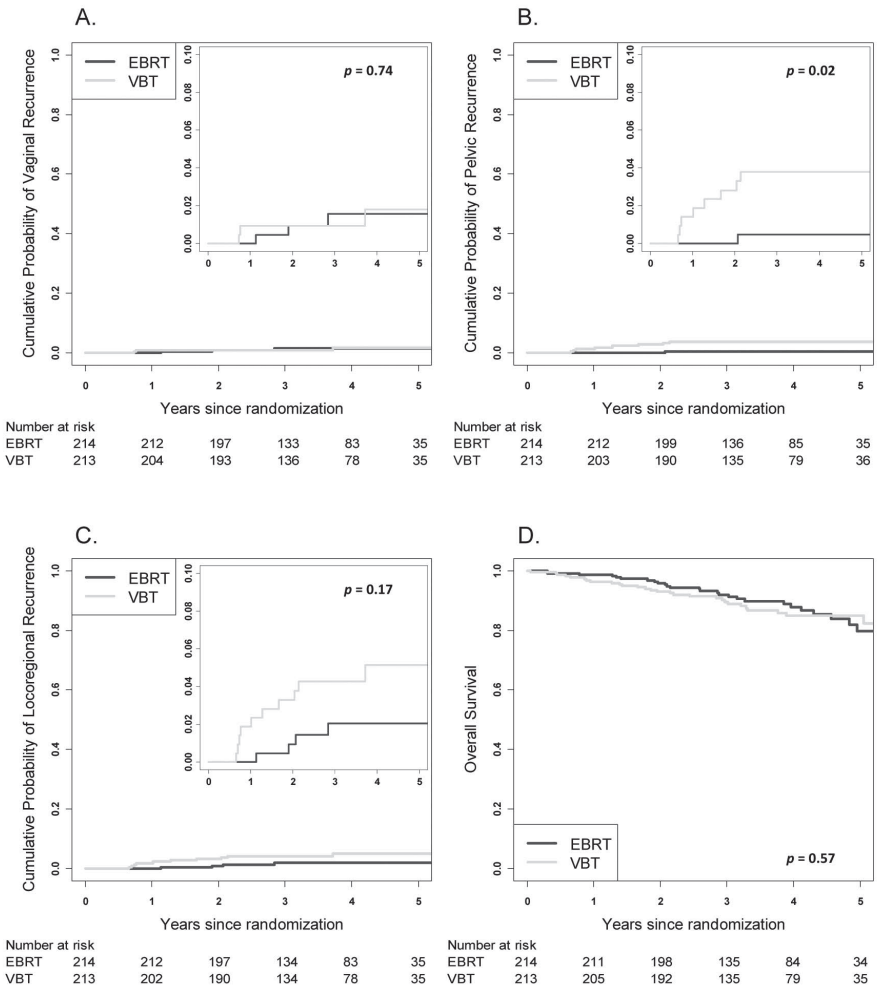


Figure 2. Cumulative probability of vaginal recurrence (A), pelvic recurrence (B), locoregional recurrence (C), and Kaplan-Meier survival curve for overall survival (D). Inserts show curves with adjusted axis from 0 to 10%. EBRT= external beam radiotherapy. VBT= vaginal brachytherapy.

Role of funding source:

The sponsor of the study reviewed and approved the design of the trial and funded data management. The sponsor had no role in data collection, data interpretation, data analysis, or writing of the report. The central data manager, principal and associate investigators, and trial statistician had full

access to the data. The decision to submit for publication was made after presentation and discussion with the trial management group (co-investigators, trial statisticians, trial coordinator, and trial pathologist).

Table 3. Recurrence and survival for true-HIR patients after pathology review (N=366).

	Events/Total	Estimated 5-year % (95% CI)	Hazard Ratio (95% CI)*	Log-rank *p* value*
Vaginal Recurrence				
EBRT	4/183	1.9 (0.6 - 5.8)	1	0.39
VBT	2/183	1.5 (0.4 - 6.5)	0.48 (0.09-2.64)	
Pelvic Recurrence				
EBRT	1/183	0.6 (0.1 - 4.0)	1	0.06
VBT	6/183	3.3 (1.5 - 7.3)	6.10 (0.73-50.7)	
Locoregional Recurrence				
EBRT	5/183	2.4 (0.9 - 6.5)	1	0.42
VBT	8/183	4.8 (2.4 - 9.7)	1.58 (0.52-4.86)	
Distant Metastases				
EBRT	10/183	5.0 (2.6 - 9.4)	1	0.79
VBT	11/183	6.4 (3.6 - 11.5)	1.12 (0.48-2.64)	
Disease Free Survival				
EBRT	24/183	80.2 (71.4 - 89.0)	1	0.89
VBT	25/183	84.5 (78.6 - 90.4)	1.04 (0.59-1.82)	
Overall Survival				
EBRT	19/183	82.1 (73.5 - 90.7)	1	0.66
VBT	22/183	86.2 (80.5 - 91.9)	1.15 (0.62-2.13)	

EBRT: external beam radiotherapy, VBT: vaginal brachytherapy
**Both log-rank tests and Cox proportional hazards models are stratified for FIGO stage.*

Results

Figure 1 shows the trial profile. 427 patients were randomly allocated to EBRT (n=214) or VBT (n=213). Data were frozen for analysis on 19 May 2009 and all patients were entered in the intention-to-treat analysis. Patient and tumour characteristics were well balanced between the groups (table 1). Table 2 shows radiotherapy details.

23 (5%) protocol violations occurred, of which 12 (3%) were major (seven in EBRT group, five in VBT group). Eleven patients did not receive the allocated treatment, one of whom died of cardiac arrest before the start of the first treatment (figure 1). Two patients received a higher brachytherapy dose (11 Gy and 10 Gy per session), because of inaccuracies while introducing a new treatment planning system at that centre.

At median follow-up of 45 months (range 18-78 months), four vaginal recurrences had been diagnosed after EBRT and three after VBT. Estimated 5-year vaginal recurrence rates were 1.8% (95% CI 0.6 – 5.9%) after VBT and 1.6% (95% CI 0.5 – 4.9%) after EBRT (log-rank p=0.74; figure 2, table 3). The HR

for vaginal recurrence after VBT compared with EBRT was 0.78 (95% CI 0.17-3.49), indicating that a true hazard ratio of 3.5 is highly unlikely. A true hazard ratio of 3.5 corresponds with an absolute difference of 4.8% (i.e. 2% after EBRT versus 6.8% after VBT), which reliably excludes the clinically relevant difference in vaginal recurrence rate of 6% that the trial aimed to exclude. We recorded no significant difference in 5-year locoregional recurrence, despite a higher rate of pelvic recurrence after VBT (table 3). Moreover, first failure analysis showed that most patients with pelvic recurrence had simultaneous distant metastases (table 3). Five-year rates of distant metastases did not differ significantly between groups (table 3).

55 patients died: 26 after EBRT and 29 after VBT. Of the 26 patients assigned to EBRT who died, 16 (62%) died from intercurrent diseases and ten (38%) from endometrial cancer. Of the 29 patients assigned to VBT who died, 14 (48%) died from intercurrent diseases and 15 (52%) from endometrial cancer. Overall and disease-free survival at 5 years were 84.8% (95% CI 79.3 – 90.3) and 82.7% (76.9 – 88.6), respectively, for VBT and 79.6% (71.2 – 88.0) and 78.1% (69.7 – 86.5), respectively, for EBRT, with overlapping survival curves (Figure 2).

Central pathology review of 367 (86%) of the patients had been completed at the time of analysis (183 [86%] patients in the EBRT group and 184 [86%] in the VBT group). Tumour grading showed poor reproducibility, especially for grade 2 (Kappa 0.34), which is consistent with previous studies. Shifts were mainly detected from grade 2 to grade 1 disease, and to a lesser extent from grade 2 to grade 3 disease (original vs. review grade 1: 48.5% [177/365] vs. 78.6% [287/365]; grade 2: 44.4% [162/365] vs. 9.0% [33/365]; grade 3: 7.1% [26/365] vs. 12.3% [45/365], with similar proportions in EBRT and VBT groups. Central review recorded 12 (3%) cases with non-endometrioid type of carcinoma (six patients in each group).

After central pathology review, 34 (8%) patients had features of high-risk disease (19 [9%] in EBRT group vs. 15 [7%] in VBT group); 27 (6%) were low risk, and therefore in retrospect ineligible (12 [6%] vs. 15 [7%]). Analysis of outcomes of the 366 patients (86%) who remained high-intermediate risk (true high-intermediate risk) at review confirmed the findings of the intention-to-treat analysis (table 4). Per-protocol analysis did not change these results

(data not shown), since there were no recurrences and only one intercurrent death in the VBT group in the six patients who had not received their allocated treatment.

A significantly higher rate of distant metastasis was recorded in patients diagnosed as high risk, or with more advanced stages, or both, after pathology review than in cases with true high-intermediate risk (25.6% [95% CI 9.7 – 41.5] at 5 years, vs. 5.8% [3.3 – 8.3], p<0.0001), with significantly lower overall survival (57.6% [37.4 – 77.8] vs. 84.2% [79.1 – 89.3], p<0.0001) and disease-free survival (54.2% [31.6 – 75.0] vs. 82.4% [77.1 – 87.7], p<0.0003), without differences between the EBRT and VBT groups.

Grade 1 and 2 gastrointestinal (EORTC-RTOG small/large intestine) toxic effects increased significantly at completion of EBRT compared with VBT (EBRT 53.8% [112/208] vs. VBT 12.6% [27/215]). This difference decreased with further follow-up and lost its statistical significance after 24 months (figure 3). For patients assigned to VBT, gastrointestinal toxic effects remained at baseline level (figure 3). Late grade 3 gastrointestinal toxic effects were reported in four (2%) patients receiving EBRT and in one (<1%) receiving VBT, requiring surgery for bowel obstruction due to adhesions or fibrosis. No treatment-related deaths occurred. From 6 months onwards, grade 1 - 2 mucosal atrophy increased, with significantly more grade 2 atrophy after VBT than after EBRT (figure 3). Grade 3 atrophy (marked atrophy with or without shortening or narrowing) was reported in only 1 (<1%) patient receiving EBRT and four (2%) receiving VBT.

Discussion

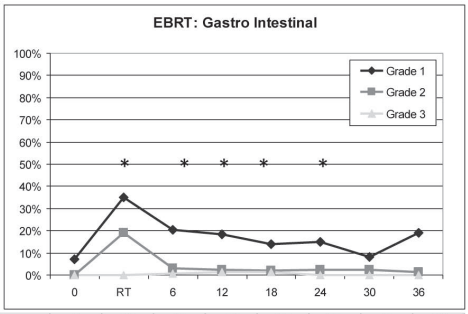
The PORTEC-2 trial compared the efficacy and toxicity of EBRT and VBT for endometrial cancer of high-intermediate risk. At a median follow-up of 45 months, very few vaginal recurrences occurred in both treatment groups, showing VBT to be very effective in ensuring of local control. The vaginal recurrence rate after EBRT is very similar to the rate of 2.2% at 5 years in the first PORTEC trial in patients at intermediate risk, showing consistency of this main finding in both trials.[2]

After PORTEC-1 and GOG#99, the indication for radiotherapy has become restricted to patients with features of high-intermediate risk, and thus most patients with endometrial cancer are treated with surgery alone (with radiotherapy as effective salvage treatment for the occasional patient with relapse). Use of radiotherapy has been justified for patients thought to be at high-intermediate risk, since radiotherapy reduces their 20% risk of locoregional recurrence to 5%, maximising initial local control and relapse-free survival. Even with no survival benefit, radiotherapy spares these patients the psychological stress of recurrence and the morbidity of intensive treatment for relapse. PORTEC-2 shows that patients at high-intermediate risk, about 30% of all patients with endometrial cancer, can be safely treated with vaginal brachytherapy alone, with fewer side-effects and improved quality of life.[11] EBRT will thus be used only for the 15% of patients with high-risk or advanced disease.

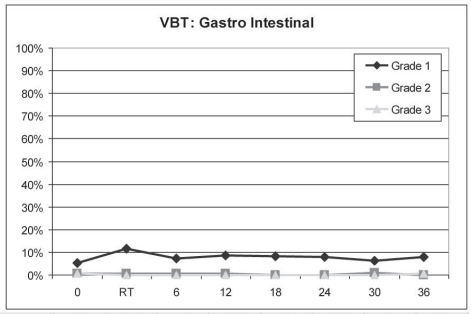
A limitation of the trial design might be that we posed a non-inferiority question, but used a design that aimed to establish the actual difference in vaginal recurrence with sufficient precision, while choosing an absolute non-inferiority margin of 6% - i.e., a power of 85% to exclude a difference in vaginal recurrence rate of 6% at 3 years. This margin of reduced efficacy of VBT was regarded as clinically acceptable in view of the absence of a survival benefit, the expected reduced toxic effects of VBT, and the fact that effective salvage treatment is available in case of vaginal recurrence.

Almost all pelvic recurrences after VBT were part of widespread disease recurrence. The rates of distant metastases were low and similar in both groups. Locoregional recurrence rates in both groups were very similar to those reported in previous randomised trials in patients with intermediate risk, which varied between 2% to 4%.[2, 3, 16, 17]

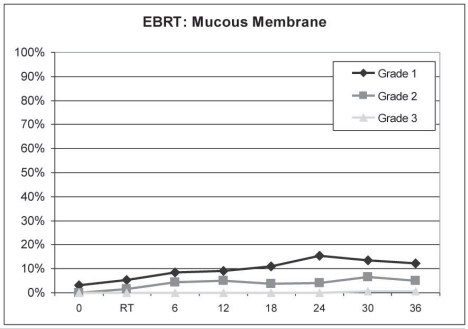
Both GOG#99 and PORTEC-1 trials showed that vaginal recurrences accounted for about 75% of recurrences in the control group.[2, 3] PORTEC-2 has shown that vaginal brachytherapy can be as effectively used for patients at high-intermediate risk to ensure vaginal control. This efficacy of VBT also explains the fairly low rate of isolated vaginal and pelvic recurrence in the control group (6.1% vs. 3.2% for EBRT) of the ASTEC/EN5 trial, the most recently reported randomised trial comparing EBRT with no additional therapy, in which 51% of



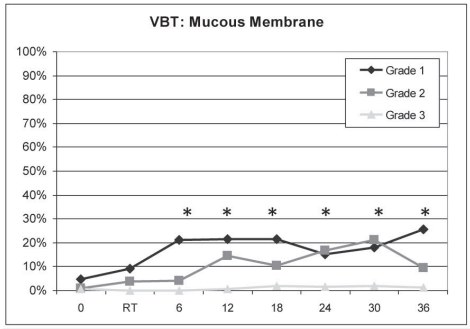
	0	RT	6	12	18	24	30	36
Grade 1	7,1%	34,9%	20,4%	18,5%	14,1%	15,0%	8,0%	19,0%
Grade 2	0,0%	18,9%	3,0%	2,5%	1,9%	2,4%	2,3%	1,2%
Grade 3	0,0%	0,0%	0,6%	1,2%	1,3%	0,0%	0,0%	0,0%



	0	RT	6	12	18	24	30	36
Grade 1	5,2%	11,5%	7,4%	8,7%	8,3%	8,0%	6,2%	8,0%
Grade 2	0,5%	0,5%	0,6%	0,6%	0,0%	0,0%	1,0%	0,0%
Grade 3	0,5%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,5%



	0	RT	6	12	18	24	30	36
Grade 1	3,3%	5,4%	8,5%	9,1%	11,0%	15,3%	13,5%	12,3%
Grade 2	0,0%	1,5%	4,3%	4,9%	3,9%	4,0%	6,7%	4,9%
Grade 3	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,5%	0,5%



	0	RT	6	12	18	24	30	36
Grade 1	4,8%	9,3%	21,1%	21,4%	21,6%	15,3%	17,9%	25,7%
Grade 2	1,0%	3,9%	4,1%	14,5%	10,5%	16,9%	21,1%	9,5%
Grade 3	0,5%	0,0%	0,0%	0,6%	1,9%	1,6%	1,9%	1,4%

*Figure 3. EORTC-RTOG early and late gastro intestinal (small/large intestine) and mucous membrane toxicity at pelvic examination. At every follow-up timepoint the toxicity rate represents the number of patients with toxicity as percentage of the total number of patients that have reached that follow-up time point. There were no grade 4 or 5 toxicities. EBRT= external beam radiotherapy. VBT= vaginal brachytherapy. RT= at completion of radiotherapy. EORTC-RTOG= European Organisation of Research and Treatment of Cancer and Radiation Therapy Oncology Group. *Time points showing significant (p<0.05) difference between EBRT and VBT.*

patients had received vaginal brachytherapy.[17] Moreover, 30% of patients in ASTEC/EN5 and all in GOG#99 underwent a staging lymphadenectomy, whereas the low rates of locoregional recurrence in PORTEC-2 were obtained without routine lymphadenectomy, which accords with the findings of randomised trials showing no survival improvement with lymphadenectomy.[18, 19]

Rates of mild-to-moderate gastrointestinal toxic effects after EBRT in the PORTEC-2 trial were similar to other randomised trials. Gastrointestinal symptoms were most pronounced during and immediately after EBRT and gradually decreased - a pattern very similar to the quality-of-life diarrhoea score. However, effect on daily activities persisted with further follow-up. Patients assigned to VBT reported very few gastrointestinal symptoms.[11]

Assessment of vaginal toxicity is complex, and some grading systems include the impact on sexual functioning (common terminology criteria for adverse events v3.0), whereas others do not (EORTC/RTOG).[14, 20, 21] For PORTEC-2 we decided to record mucosal atrophy and assess the effect of mucosal side-effects on sexual functioning with the quality-of-life sections on sexual activity and vaginal dryness. The vaginal mucosa surface dose is higher with VBT than with EBRT, leading to more grade 2 atrophy. Grade 3 atrophy (substantial atrophy with or without shortening of the vagina) was reported in only five patients (four in VBT group and one in EBRT group). Patient-reported rates of sexual activity increased during the first 6 months after treatment and remained stable thereafter, without significant differences between the treatment groups.[11] Sexual functioning and activity rates (40% at 12 months) were similar to those reported for elderly women in a population-based analysis.[22]

Central pathology review was done because previous work of our group and others had shown discordances in pathological diagnoses, with 8% discrepancies altering patient management.[4, 15] A poor reproducibility of the intermediate grade (grade 2) was confirmed. Additionally, 3% non-endometrioid histological types were diagnosed. On the basis of revised pathologic changes 86% of the patients were true high-intermediate risk, whereas 6% had low-risk and 8% high-risk features. The results of this central pathology review did not change the main outcomes of the study. However, patients shown to be at high risk at review had a significantly higher rate of distant metastasis and lower survival rates, confirming the rationale for trials that include chemotherapy for patients at high risk. In the PORTEC-3 trial, pathology review is mandatory before randomisation, and high-risk patients are randomly assigned between EBRT alone and EBRT with concurrent and adjuvant chemotherapy.

In conclusion, VBT is very effective in ensuring local control, keeping to a minimum the risk of vaginal recurrence, which is the most frequent site of disease recurrence in patients with endometrial carcinoma of high-intermediate risk. VBT achieves excellent vaginal control and rates of locoregional recurrence, overall and disease-free survival that are similar to EBRT, and quality of life and gastrointestinal toxic effects are significantly better with VBT. VBT should be the adjuvant treatment of choice for patients with endometrial carcinoma of high-intermediate risk.

Reference List

1. Bray F, Loos AH, Oostindier M, Weiderpass E. Geographic and temporal variations in cancer of the corpus uteri: incidence and mortality in pre- and postmenopausal women in Europe. Int J Cancer 2005; 117(1):123-131.
2. Creutzberg CL, van Putten WL, Koper PC et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000; 355(9213):1404-1411.
3. Keys HM, Roberts JA, Brunetto VL et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004; 92(3):744-751.
4. Scholten AN, van Putten WL, Beerman H et al. Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys 2005; 63(3):834-838.
5. Creutzberg CL, van Putten WL, Koper PC et al. The morbidity of treatment for patients with Stage I endometrial cancer: results from a randomized trial. Int J Radiat Oncol Biol Phys 2001; 51(5):1246-1255.
6. Alektiar KM, Venkatraman E, Chi DS, Barakat RR. Intravaginal brachytherapy alone for intermediate-risk endometrial cancer. Int J Radiat Oncol Biol Phys 2005; 62(1):111-117.
7. Anderson JM, Stea B, Hallum AV, Rogoff E, Childers J. High-dose-rate postoperative vaginal cuff irradiation alone for stage IB and IC endometrial cancer. Int J Radiat Oncol Biol Phys 2000; 46(2):417-425.
8. Chadha M, Nanavati PJ, Liu P, Fanning J, Jacobs A. Patterns of failure in endometrial carcinoma stage IB grade 3 and IC patients treated with postoperative vaginal vault brachytherapy. Gynecol Oncol 1999; 75(1):103-107.
9. Rittenberg PV, Lotocki RJ, Heywood MS, Krepart GV. Stage II endometrial carcinoma: limiting post-operative radiotherapy to the vaginal vault in node-negative tumors. Gynecol Oncol 2005; 98(3):434-438.
10. Weiss E, Hirnle P, Arnold-Bofinger H, Hess CF, Bamberg M. Adjuvant vaginal high-dose-rate afterloading alone in endometrial carcinoma: patterns of relapse and side effects following low-dose therapy. Gynecol Oncol 1998; 71(1):72-76.
11. Nout RA, Putter H, Jurgenliemk-Schulz IM et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol 2009; 27(21):3547-3556.
12. Shepherd JH. Revised FIGO staging for gynaecological cancer. Br J Obstet Gynaecol 1989; 96(8):889-892.
13. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007; 26(11):2389-2430.

14. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995; 31(5):1341-1346.
15. Scholten AN, Smit VT, Beerman H, van Putten WL, Creutzberg CL. Prognostic significance and interobserver variability of histologic grading systems for endometrial carcinoma. Cancer 2004; 100(4):764-772.
16. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 1980; 56(4):419-427.
17. Blake P, Swart AM, Orton J et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet 2009; 373(9658):137-146.
18. Benedetti PP, Basile S, Maneschi F et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2008; 100(23):1707-1716.
19. Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009; 373(9658):125-136.
20. ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf 2003. Trotti A, Colevas AD, Setser A et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003; 13(3):176-181.
21. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med 2007; 357(8):762-774.

4

Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the Post Operative Radiation Therapy in Endometrial Carcinoma 1 (PORTEC-1) trial.

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Abstract

Purpose: To determine the long-term outcome and health-related quality of life (HRQL) of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the Post Operative Radiation Therapy in Endometrial Carcinoma 1 (PORTEC-1) trial.

Patients and Methods: Between 1990 and 1997, 714 patients with stage IC grade 1 to 2 or IB grade 2 to 3 EC were randomly allocated to pelvic external-beam radiotherapy (EBRT) or no additional treatment (NAT). HRQL was evaluated with the Short Form 36-item (SF-36) questionnaire; subscales from the European Organisation for Research and Treatment of Cancer (EORTC) PR 25 module for bladder and bowel symptoms, and the CX 24 and OV28 modules for sexual symptoms; and demographic questions. Analysis was by intention-to-treat.

Results: Median follow-up was 13.3 years. The 15-year actuarial locoregional recurrence rates were 5.8% for EBRT versus 15.5% for NAT ($p<0.001$), and 15-year overall survival was 52% versus 60% ($p=0.14$). Of the 351 patients confirmed to be alive with correct address, 246 (70%) returned the questionnaire. Patients treated with EBRT reported significant ($p<0.01$) and clinically relevant higher rates of urinary incontinence, diarrhea and fecal leakage, leading to more limitations in daily activities. Increased symptoms were reflected by the frequent use of incontinence materials after EBRT (day and night use 42.9% vs. 15.2% for NAT, $p<0.001$). Patients treated with EBRT reported lower sores on the SF-36 scales 'physical functioning' ($p=0.004$) and 'role-physical functioning' ($p=0.003$).

Conclusions: EBRT for endometrial cancer is associated with long-term urinary and bowel symptoms, and lower physical and role-physical functioning, even 15 years after treatment. Despite its efficacy in reducing locoregional recurrence, EBRT should be avoided in patients with low- and intermediate-risk EC.

Introduction

Four randomized trials have established the role of radiotherapy in intermediate risk endometrial carcinoma (EC).1-4 The Post Operative Radiation Therapy in Endometrial Carcinoma 1 (PORTEC-1) trial (1990-1997) was among the first to randomly compare pelvic external beam radiotherapy (EBRT) to no additional treatment (NAT), and it showed that EBRT provides a highly significant improvement of local control, but without a survival advantage.3;5 Furthermore, EBRT was associated with 26% risk of adverse effects, mainly grade 1-2 GI toxicity.6

It was concluded that in view of the absence of survival benefit, EBRT would only be justified for patients at relatively high risk of recurrence. The risk factors identified were: grade 3, age 60 years or older, and deep myometrial invasion. Patients with at least 2 of these 3 risk factors were designated high-intermediate risk (HIR). Patients with HIR features had 20% risk of locoregional recurrence (LRR) after NAT, which was reduced to 5% with EBRT.3;5 For these HIR patients the indication for radiotherapy (RT) was maintained after PORTEC-1, although EBRT was abandoned for the 50% of patients with stage I EC who were designated low-intermediate risk (LIR).

The PORTEC-2 trial (2002-2006) confirmed that EBRT could safely be substituted by vaginal brachytherapy (VBT) for HIR patients.7;8 After a median follow-up of 24 months HRQL analysis showed that bowel symptoms such as diarrhea and fecal leakage were significantly increased after EBRT, leading to more limitation in daily activities and a significant lower level of social functioning.7 Only a few studies9-13 have investigated long-term HRQL of EC survivors, and most studies included few patients or had low (<40%) response rates. One retrospective study with an adequate response rate (75%) found that EBRT was negatively associated with vitality and physical and social well-being, but scores were similar to those of an age matched population.14

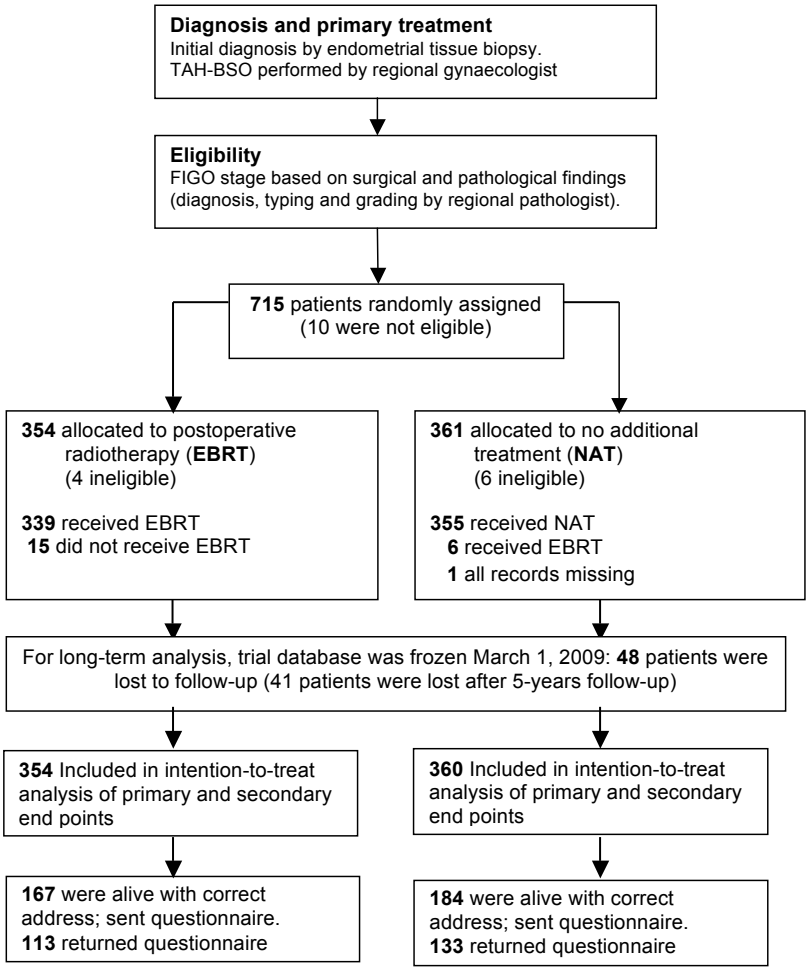
The short-term PORTEC-2 findings prompted this analysis of long-term HRQL of EC survivors treated in the PORTEC-1 trial 11-18 years ago to investigate whether the impact of EBRT would have resolved over time.

Patients and Methods

Between 1990 and 1997, 714 patients with stage I EC participating in the PORTEC-1 trial were randomly allocated to EBRT or NAT. Information on patient selection and treatment have been provided in previous publications3;5;6 and in the CONSORT diagram (Fig 1.). Surgery consisted of total extrafascial hysterectomy and bilateral salpingo-oophorectomy without lymphadenectomy (only biopsy of any suspicious lymph nodes). Women of any age with a WHO performance score 0 to 2; endometrial adenocarcinoma stage I, grade 1 with deep (³50%) myometrial invasion, grade 2 with any invasion, or grade 3 with superficial (<50%) invasion were eligible. Informed consent was obtained from all patients. Pelvic EBRT was administered with the target volume including the parametrial tissues, proximal two-thirds of the vagina, and lymphatic drainage regions along the internal iliac vessels up to the promontory. The superior field border was at the L5-S1 disc. Total dose was 46 Gy with 2 Gy daily fractions. The original trial protocol was approved by the Protocol Review Committee of the Dutch Cancer Society and by the Ethics Committees of the participating centers. Because HRQL investigation was not included in the original protocol, ethics approval for the current study was sought and obtained in 2007 from the Ethics Committee of Leiden University Medical Center.

Patients were followed in their regional hospitals at least until 7 years after treatment. LRRs were confirmed by histology. Patterns of failure were recorded by sites of failure: locoregional, distant or both. LRRs were defined as vaginal and/or pelvic recurrences. Distant failures included para-aortic lymph node metastases, abdominal relapses, liver, lung, and bone metastases and diffuse metastatic disease. For this analysis, vital status of all patients considered to be alive and disease-free according to the trial database was checked with the Dutch Bureau for Genealogy and the governmental local population administration (GBA). Patients confirmed to be alive (N=428; January 2008) and for whom a correct mailing address was available (N=351) were sent a questionnaire to evaluate long-term HRQL. The questionnaire was accompanied by a letter written by each patient's own radiation oncologist explaining the background and purpose of the questionnaire. A reminder

CONSORT diagram. TAH-BSO: total abdominal hysterectomy and bilateral salpingo-oophorectomy; FIGO: International Federation of Gynecology and Obstetrics; EBRT: external beam radiotherapy; NAT: no additional treatment; HRQL: health related quality of life. Follow-up and HRQL patient selection



was sent to patients who had not returned the questionnaire after 3 months. Patients who returned the questionnaire were noted alive with the date of completing their questionnaire. For patients who did not respond, vital status was noted as on the date of GBA confirmation. For patients who had died the date of death according to GBA registry was noted and local study coordinators were contacted to obtain causes of death. Follow-up information was updated, especially for patients with previously known recurrences and those who noted events on their questionnaires, by obtaining information from their local hospital or general practitioner.

HQRL assessment

General health status was measured with the Dutch version of the Medical Outcomes Study Short Form 36-item Health Survey (SF-36).[16] The scores were standardized on a scale from 0 to 100, with higher scores indicating better health status. To compare the health status of survivors with a norm population, we used age matched SF-36 scores available from the general Dutch female population.[17]

Although an EC module has recently been developed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group[18], no EC-specific symptom questionnaire was available at the time of this study. With approval of the EORTC Quality of Life Group, relevant subscales from EORTC modules were combined into a symptom module, similar to that used in the PORTEC-2 trial.[7] Subscales for bowel and bladder symptoms from PR25, for sexual functioning and symptoms from OV28, and additional single items from CX24 were used.[19-21] For all items Likert-type response scales were used, with a 4 point response scale. All subscales and individual item responses were linearly converted to 0 to 100 scales. Higher scores for functioning items represent a better level of functioning. For the symptom items, a higher score reflects a higher level of symptoms and decreased quality of life.

The impact of cancer (IOC) questionnaire, a specific questionnaire assessing the long-term impact of diagnosis and treatment of cancer, was also included in the survey.[22;23] Since analysis of the IOC did not show differences between both treatment groups the results are not further discussed in this paper.

Statistical methods

All statistical analyses were performed using SPSS, version 17.0 (SPSS, Inc, Chicago, IL). Primary endpoints for the study were LRR and overall survival (OS). The analysis was by intention to treat. All randomly assigned patients were kept in the analysis, including those who did not meet eligibility criteria (n=10) or with protocol violations (n=31). The Kaplan–Meier method, logrank test and Cox regression analysis were used for time-to-event analyses with the following endpoints: LRR and distant metastasis from randomization with censoring at date of last contact or death; OS from randomization with failure defined as death irrespective of the cause and censoring at the date of last contact for patients alive.

Chi-square statistics or Fisher's exact test for categorical variables and *t* test for continuous variables (p=0.05 was considered significant) were used to compare patient and tumor characteristics of EBRT with NAT and respondents with non-respondents. Explanatory comparison of HRQL scores was done with the *t* test; descriptive mean scores are presented in the Tables. To guard against false positive results due to multiple testing, a two sided *p*-value of 0.01 was considered statistically significant. Differences between the groups were considered clinically relevant if they exceeded of 10 points on a scale of 100 points.[24] Amount of variance explained (R^2) by EBRT was analyzed in a linear regression model with age, co-morbidity and treatment arm entered in this order (Figure 2).

Results

Fifteen-year outcomes

The outcome analysis was done on data frozen on March 1, 2009. Of the 714 evaluable patients, 48 patients were lost to follow-up (41 of them were lost after >5 years of follow-up); they were included in the analysis and censored at the date of last follow-up (Fig 1). Median follow-up for patients alive was 13.3 years (range, 2.8 to 18.5 years). The study groups were well balanced with regard to patient and tumor characteristics.[3] LRRs at 15-years were 5.8% in the RT group and 15.5% in the NAT group (hazard ratio [HR], 3.46; 95% CI 1.93 to 6.18; logrank test p< 0.0001; Figure 3). Among 50 LRRs in the NAT arm, 37

Table 1. Scores on Medical Outcomes Study Short Form 36-item Health Survey (SF-36) and EORTC module

	EBRT (n=113) mean ± SD	NAT (n=133) mean ± SD	*p*-value*	Recurrence after NAT (n=14) mean ± SD	*p*-value†
SF-36					
General Health	58 ± 22	62 ± 17	0.082	67 ± 18	0.311
Physical Function	**50 ± 30**	**62 ± 27**	**0.004**	62 ± 22	0.973
Role-Physical	**40 ± 44**	**59 ± 45**	**0.003**	66 ± 48	0.572
Bodily Pain	**62 ± 27**	**70 ± 23**	**0.009**	70 ± 22	0.999
Vitality	57 ± 30	62 ± 19	0.055	60 ± 17	0.744
Social Functioning	*71 ± 29*	*79 ± 24*	*0.030*	77 ± 24	0.817
Role-emotional	*64 ± 47*	*77 ± 36*	*0.033*	83 ± 24	0.579
Mental Health	71 ± 22	73 ± 18	0.526	81 ± 15	0.135
Physical Component Scale	*38 ± 12*	*42 ± 11*	*0.014*	42 ± 13	0.794
Mental Component Scale	51 ± 12	52 ± 10	0.614	53 ± 9	0.745
Urinary Symptoms					
Frequency during the day	*47 ± 31*	*37 ± 31*	*0.015*	42 ± 29	0.601
Frequency during the night	*48 ± 27*	*39 ± 27*	*0.017*	45 ± 34	0.416
Urinary urgency	**46 ± 33**	**32 ± 32**	**0.001**	47 ± 33	0.078
Sleep deprivation because of US	21 ± 27	20 ± 30	0.716	27 ± 36	0.395
Need to remain close to toilet	**26 ± 32**	**10 ± 20**	**<0.001**	18 ± 31	0.392
Incontinence for urine	**30 ± 31**	**16 ± 23**	**<0.001**	27 ± 25	0.090
Dysuria	6 ± 16	6 ± 16	0.810	12 ± 22	0.344
Difficulty with voiding	16 ± 25	11 ± 22	0.121	12 ± 31	0.876
Limitation daily activities US	**11 ± 21**	**4 ± 13**	**0.006**	3 ± 10	0.755
Bowel Symptoms					
Limitation daily activities BS	**26 ± 34**	**15 ± 26**	**0.006**	33 ± 36	0.062
Fecal urgency	**44 ± 37**	**25 ± 33**	**<0.001**	**64 ± 32**	**<0.001**
Fecal leakage	**19 ± 30**	**8 ± 19**	**0.002**	*28 ± 30*	*0.021*
Diarrhea	**25 ± 33**	**10 ± 20**	**<0.001**	21 ± 29	0.165
Rectal blood loss	2 ± 11	1 ± 5	0.416	3 ± 10	0.441
Bloated feeling	18 ± 27	13 ± 23	0.199	9 ± 16	0.505
Flatulence	30 ± 29	26 ± 29	0.240	45 ± 43	0.129
Abdominal cramps	*20 ± 28*	*12 ± 21*	*0.011*	15 ± 26	0.512
Vaginal Symptoms					
Vaginal irritation	9 ± 19	9 ± 19	0.993	22 ± 30	0.112
Vaginal discharge	5 ± 15	4 ± 13	0.523	18 ± 31	0.136
Vaginal blood loss	1 ± 5	1 ± 4	0.816	6 ± 13	0.167
Sexual Functioning					
Sexual interrest	14 ± 20	10 ± 18	0.212	3 ± 11	0.079
Sexual activity	11 ± 18	8 ± 17	0.393	4 ± 11	0.394
Sexual Symptoms					
Sexual enjoyment	36 ± 28	31 ± 27	0.532	17 ± 33	0.255
Vaginal dryness	33 ± 38	26 ± 30	0.384	8 ± 17	0.229
Body Image					
Decreased feeling of attractiveness	9 ± 22	5 ± 15	0.093	6 ± 19	0.888
Less feminine	6 ± 18	3 ± 11	0.180	0 ± 0	0.002
Dissatisfied with body	17 ± 27	11 ± 19	0.094	15 ± 23	0.481
Remaining Single Items					
Lymphoedema	22 ± 30	20 ± 26	0.590	21 ± 31	0.882
Pain lower back	33 ± 36	24 ± 30	0.054	24 ± 34	0.978
Hot flushes	16 ± 28	9 ± 22	0.060	11 ± 22	0.758

*EBRT: external beam pelvic radiotherapy; NAT: no additional treatment; US: urinary symptoms; BS: bowel symptoms; EORTC: European Organistation for Research and Treatment of Cancer; SD: standard deviation. *EBRT vs NAT, there were no differences when excluding patients with a recurrence and/or with second cancer.P-values <0.01 are shown in bold, <0.05 in italic. †patients with a recurrence after NAT vs patients without a recurrence after NAT*

(74%) were located in the vagina. The 15-year rate of distant metastases was similar in the treatment groups: 9.3% for EBRT and 7.1% for NAT (HR, 0.73; 95% CI 0.43 to 1.25; logrank test p=0.25). Overall survival (OS) rate at 15 years was 52% after EBRT vs. 60% after NAT (HR, 0.84; 95% CI 0.67 to 1.06; logrank test p=0.94; Figure 1).

HRQL population and compliance

Quality-of-life questionnaires were sent to 351 patients of whom the correct address could be confirmed. In all, 246 patients (70%) responded to the questionnaire. Median follow-up of the respondents was 13.3 years (range 9.4-18.3 years). Nonrespondents were slightly older; all other tumor and treatment characteristics were equally balanced between responders and non-respondents and between the EBRT and NAT groups (Table 2). As expected, more respondents in the NAT arm had been diagnosed with a locoregional recurrence (N=14) than in the EBRT arm (N=1; p=0.007); there were no significant differences in the rates of second cancers or distant metastases between respondents in both arms.

Six patients returned the questionnaire only responding to the demographic questions. Excluding these six patients, the rate of missing data was 8.7% for the SF-36, 5.3% for EORTC items, and 7.4% for IOC. Patients were more reluctant in responding to questions about their sexual functioning (activity and interest: 29% missing). Among the patients who indicated they were sexually active, 91% responded to the items on sexual symptoms. Overall, the treatment groups did not differ significantly with regard to questionnaire response rates and missing items.

General health status (SF-36)

Patients treated with EBRT reported lower scores on all scales of the SF-36 (Table 1 and Fig 4). These differences were significant and clinically relevant for physical functioning (EBRT, 50.5 vs. NAT, 61.6, p=0.004) and role-physical (EBRT, 40.3 vs. NAT, 58.5, p=0.003).

EBRT was a significant explanatory variable for deteriorated score on the physical functioning scale (R2 change, 3.0%; p=0.002) and role-physical scale (R2 change, 3.1%; p=0.006) after correction for age and co-morbidity (Fig 2).

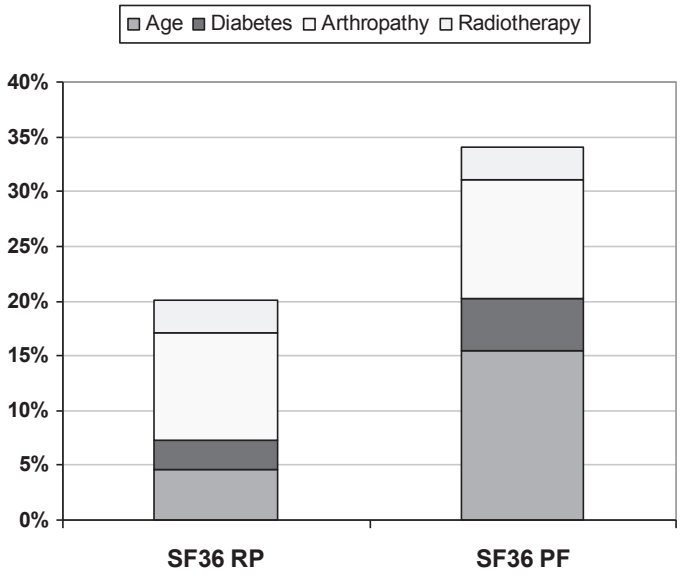


Figure 2. Percentage of explained variance in scores for all patients on Short Form 36-item (SF-36) Role-Physical (RP) and Physical Functioning (PF). Light-blue represents the percentage of variance in the SF-36 score that is explained by the addition of radiotherapy, after correction for age and co-morbidity (arthropathy and diabetes as significantly explanatory variables).

There were no clinically relevant differences between the SF-scores of either of the treatment groups and those of an age-matched Dutch norm population (data not shown).

Symptom items (EORTC modules)

Compared with patients in the NAT arm, patients treated with EBRT reported significantly higher levels of urinary urgency (mean, 45.6 vs. 31.7; $p<0.001$), and of urinary incontinence, a higher need to remain close to the toilet and more limitations in daily activities due to bladder symptoms (Table 1 and Figure 5).

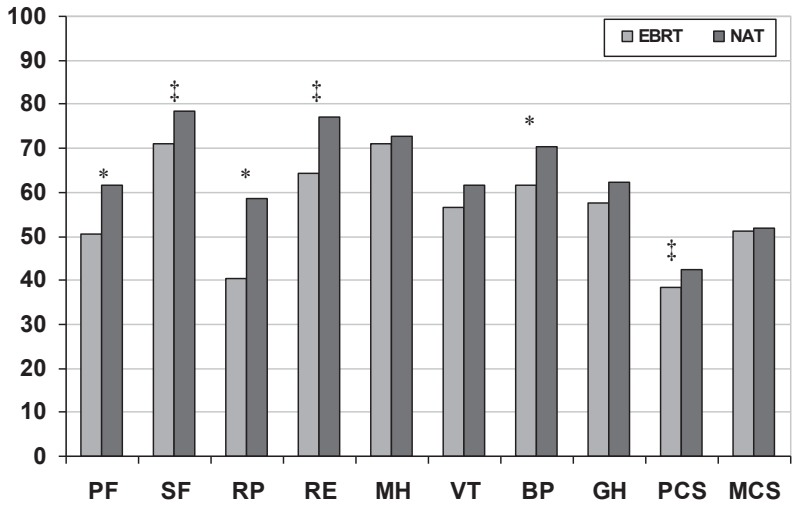


*Figure 4. Scores of both treatment groups on Medical Outcomes Study Short Form 36-item Health Survey. EBRT, external beam pelvic radiotherapy; NAT, no additional treatment; PF, physical functioning; SF, social functioning; RP, role-physical; RE, role-emotional; MH, mental health; VT, vitality; BP, bodily pain; GH, general health; PCS, physical component scale; MCS, mental component scale. * p-values ≤0.01, ‡ p-values ≤0.05*

As for bowel symptoms, patients treated with EBRT reported increased levels of diarrhea, fecal leakage and more limitations in daily activities due to bowel symptoms (25.8 vs. 14.6; p=0.006). As a result of these increased symptoms, significantly more patients treated with EBRT indicated they used incontinence materials. "Day and night usage" was reported by 42.9% of patients treated with EBRT, in contrast to 15.2% of patients who had NAT, and "never use" was reported by 39.0% vs. 60.0% (overall p<0.001).

There were no significant differences in vaginal symptoms, body image, lymph edema, lower back pain or menopausal symptoms between the groups. Among the patients that answered questions on their sexual functioning and symptoms, 24.3% reported being sexually active, with no differences in functioning or symptoms between the EBRT and NAT group.

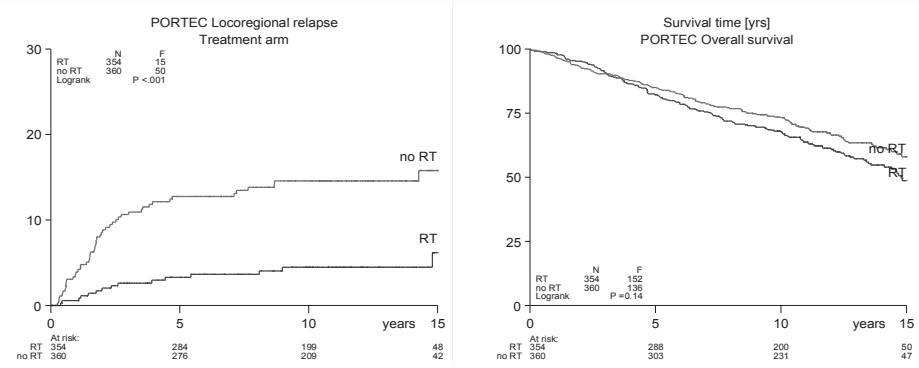


Figure 3. Probability of locoregional (vaginal and/or pelvic) relapse (left) and overall survival (right) for patients assigned to postoperative radiotherapy (RT) or no additional treatment (no RT). N, number of patients; F, number of events

HRQL after having survived a locoregional recurrence or a second cancer

Patients who had survived a locoregional recurrence in the NAT-arm (n=14) reported significantly more fecal urgency and fecal leakage, with a trend towards more urinary urgency and urinary incontinence on the EORTC items, compared with the other patients who had NAT, although there were no significant differences between the patients who had a recurrence after NAT and the EBRT patients (Table 1).

A sensitivity analysis was undertaken to estimate a possible effect of having survived a recurrence or a second cancer on the main HRQL analysis. In this analysis, HRQL outcomes were compared between both treatment arms after exclusion of patients with a recurrence and/or a second cancer. This analysis did not alter the previously described findings.

Discussion

This analysis of the long-term outcomes of the PORTEC-1 trial confirms the highly significant reduction of locoregional recurrence obtained by pelvic EBRT, but any survival benefit is absent. EBRT was found to be associated with a clinically relevant increase of patient reported long-term bowel and bladder symptoms, most notably urinary urgency, incontinence, diarrhea and fecal

Table 2. Patient, tumor and treatment characteristics of HRQL respondents.

	EBRT		NAT		
	N	**%**	**N**	**%**	***p*-value**
	113	46	133	54	
Age, mean (range)	75.5	(56-94)	76.0	(59-93)	0.64
≤70	36	32	28	21	0.02
71-80	38	34	68	51	
>80	39	34	37	28	
Maritial status					
Married	54	50	57	44	0.54
Not Married	12	11	14	11	
Divorced	6	6	5	4	
Widow	35	33	54	41	
Partner and living together					
Yes, together	42	46	54	45	0.68
Yes, living apart	0	0	1	1	
No	50	54	66	54	
Children					
Yes	81	76	91	72	0.41
No	25	24	36	28	
Living with children					
Yes	7	8	8	8	0.98
No	77	92	87	92	
Comorbidities					
Asthma	15	14	9	7	0.08
Heart disease	10	9	7	6	0.26
Hypertension	44	41	66	52	0.10
Stroke	6	6	3	2	0.20
Kidney disease	4	4	1	1	0.12
Diabetes	26	24	23	18	0.26
Malignancy	5	5	2	2	0.17
Arthropathy	48	44	53	41	0.64
Skin disease	3	3	9	7	0.14
Liver disease	1	1	1	1	0.90
Thyroid disease	8	7	6	5	0.38
No comorbidity	17	16	14	11	0.28
Medication for comorbidity					
Yes	79	76	97	81	0.59
No	25	24	23	19	
Grade					
1	90	80	103	77	0.13
2	14	12	10	8	
3	9	8	20	15	
Myometrial infiltration					
<50%	45	40	61	46	0.34
>50%	68	60	72	54	
FIGO stage and grade					
IB grd 2	40	35	52	39	0.53
IB grd 3	5	4	9	7	
IC grd 1	21	19	28	21	
IC grd 2	47	42	44	33	

Age and demografic characteristics at time of questionnaire; tumor characteristics of randomisation (before central pathology review).
EBRT: external beam pelvic radiotherapy; NAT: no additional treatment

urgency and leakage, compared with surgery alone. These symptoms resulted in more limitations of daily activities. The increased symptom rates are reflected by the frequent use of incontinence materials after EBRT. Moreover, patients

treated with EBRT reported significant and clinically relevant lower physical and role-physical functioning (the extent to which role-related activities are limited by physical functioning).

As expected, there were more patients in the NAT group who had survived a locoregional recurrence and had undergone salvage therapy.[25] These patients reported higher levels of fecal urgency and fecal leakage, with a trend towards more urinary urgency and urinary incontinence, similar to the patients in the EBRT group.

Randomized controlled trials on adjuvant RT for EC have published acute toxicity rates after EBRT of approximately 60% (predominantly grade 1-2 GI), although late toxicity rates show a decline to approximately 20% grade 1-2 symptoms at 5 years and overall 3% grade 3-4 late complications.[4;6;26] Patient-reported toxicity outcomes that providing insight in the impact of low-grade toxicity on HRQL are lacking in these trials, and follow-up of reported toxicity generally does not exceed 5 years.

The 2-year HRQL results of the PORTEC-2 trial showed that bowel symptoms (diarrhea, fecal leakage) were significantly increased in patients treated with EBRT, leading to a higher need to remain close to a toilet and a higher level of limitation of daily activities due to bowel problems, which resulted in a significant lower level of social functioning for these patients compared with patients who received brachytherapy.[7] These short-term results reflect the long-term HRQL findings of PORTEC-1, suggesting that although the negative impact of EBRT decreases in the first 6 months after treatment, there is a long-term component that persists during subsequent years. The few retrospective studies that evaluated long-term patient reported symptoms after pelvic radiotherapy confirm the increased rate of prolonged bowel and bladder symptoms after radiotherapy.[15;27;28] The increase of urinary incontinence and fecal leakage after EBRT are suggestive for a decreased pelvic floor function, although the exact etiology remains unclear. In addition to the chronic effects of radiation to the gastro intestinal epithelium, a recent study in prostate cancer patients found that besides dose volume parameters regarding the anal sphincter, colonic dismotility resulting in a faster colonic transit and reduced rectal compliance contribute to anorectal dysfunction.[29;30]

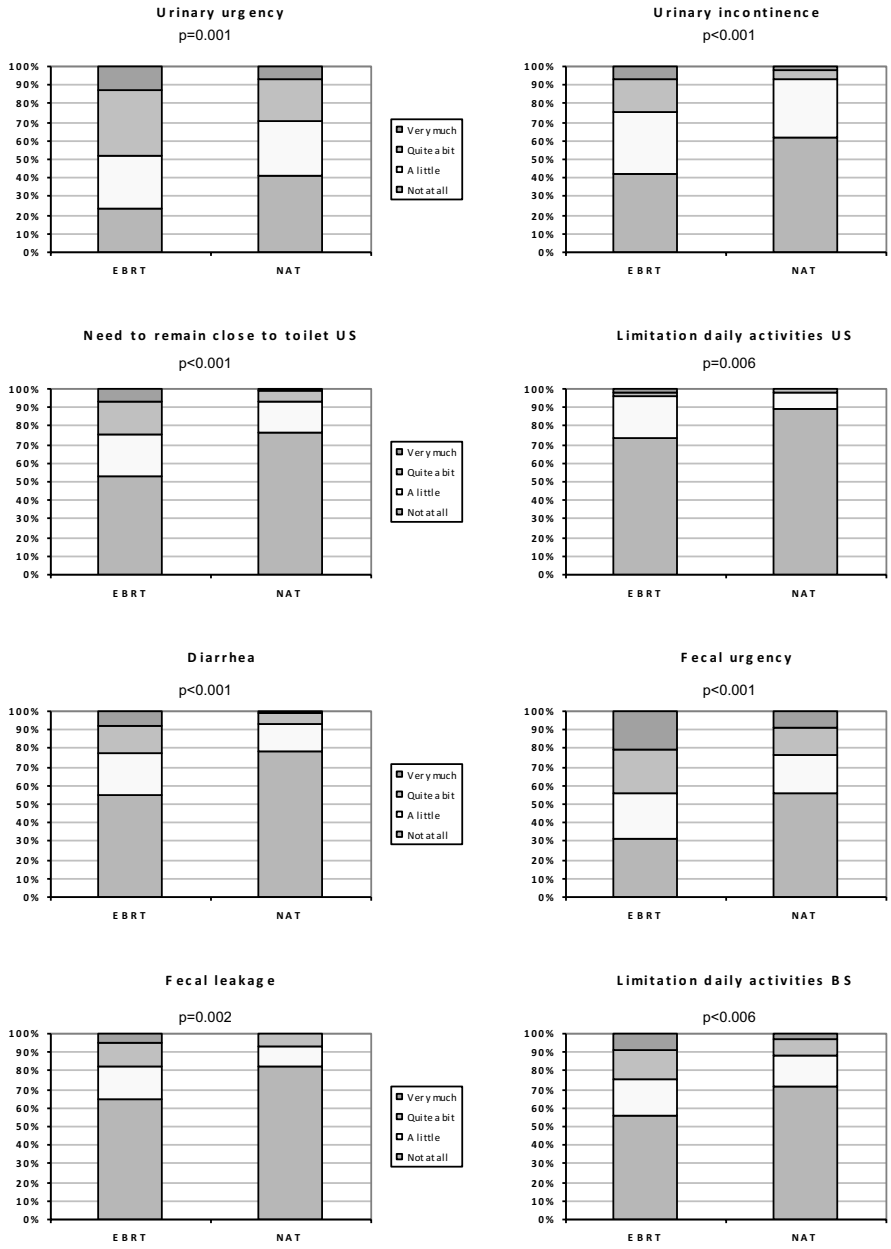


Figure 5. Patient responses to single-item symptom scores of urinary urgency, urinary incontinence, need to remain close to the toilet due to urinary symptoms (US), limitation in daily activities due to US and bowel symptoms (BS), diarrhea, fecal urgency and fecal leakage. EBRT, external beam pelvic radiotherapy; NAT, no additional treatment.

Techniques for radiation therapy have improved over the last two decades, first the introduction of 3D-conformal RT as a standard, and the more recent introduction of intensity-modulated RT (IMRT), with significantly improved bowel sparing.[31] Approximately 52% of the patients in PORTEC-1 were treated with a four-field box technique and 18% with a 3-field technique with some form of individualized shielding, although 30% were treated with parallel opposing fields. The use of multiple fields was associated with a lower rate of late complications compared to parallel opposing fields.[6] Standard use of IMRT might further decrease the rate of late radiation toxicity. However, even with sophisticated IMRT techniques the target volume for gynecological cancers remains relatively large, with significant exposure of bowel, rectum, bladder and pelvic floor muscles to the full radiation dose. This necessitates research into etiology and preventive measures.[32;33]

One of the most illustrative results of this long-term HRQL analysis is the increased use of incontinence materials among patients treated with EBRT. The prevalence of incontinence among the general population of elderly women in the Netherlands is 30-40%, with higher rates among women with comorbid conditions such as diabetes.[34] In our study, urinary incontinence was reported by 38.2% of the patients in the NAT arm, much in line with the general population, in contrast to 57.8% of the EBRT patients. After EBRT significantly more women used incontinence materials during the day and at night (EBRT, 42.9% vs. NAT, 15.2%; $p<0.001$).

Sexual functioning has long been identified as an important part of quality of life after cancer treatment.[35] In this group of elderly women (median age 76 years), 24.3% reported to be sexually active, which is in accordance with population data.[36] There were no differences between both treatment groups with regard to sexual functioning or symptoms.

The abandonment of EBRT for the 55% patients who had EC and LIR features has been confirmed to be a correct decision. Adverse effects of EBRT have a long-term negative impact on HRQL and EBRT can therefore not be justified in absence of survival benefit and in presence of effective salvage RT for the very few LIR patients who develop locoregional recurrence.

For patients with HIR features the indication for RT was maintained. For these patients the subsequent PORTEC-2 trial has shown that VBT was highly effective, with fewer side effects and better HRQL.[8] As a result of the PORTEC-2 trial, HIR patients are currently treated with VBT, thus sparing a further 30% of patients with EC the risks and morbidity of EBRT.

According to the PORTEC-1 and PORTEC-2 data, EBRT has remained indicated as adjuvant therapy only for the 15% of patients with EC who have high-risk features. Several randomized trials (PORTEC-3, Gynecologic Oncology Group [GOG]-249, GOG-258) are currently investigating the role of chemotherapy for patients with high-risk EC.

In conclusion, pelvic EBRT for EC is associated with long-term urinary and bowel symptoms, leading to lower physical and role-physical functioning, even 15 years after treatment. Combined with the 15-year outcome results of the PORTEC-1 trial, it is clear that EBRT should be avoided in patients with low- and intermediate-risk EC.

References

1. Aalders J, Abeler V, Kolstad P et al: Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 56:419-427, 1980
2. Blake P, Swart AM, Orton J et al: Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet 373:137-146, 2009
3. Creutzberg CL, van Putten WL, Koper PC et al: Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 355:1404-1411, 2000
4. Keys HM, Roberts JA, Brunetto VL et al: A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 92:744-751, 2004
5. Scholten AN, van Putten WL, Beerman H et al: Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys 63:834-838, 2005
6. Creutzberg CL, van Putten WL, Koper PC et al: The morbidity of treatment for patients with Stage I endometrial cancer: results from a randomized trial. Int J Radiat Oncol Biol Phys 51:1246-1255, 2001
7. Nout RA, Putter H, Jurgenliemk-Schulz IM et al: Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol 27:3547-3556, 2009
8. Nout RA, Smit VT, Putter H et al: Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 375:816-823, 2010
9. Bradley S, Rose S, Lutgendorf S et al: Quality of life and mental health in cervical and endometrial cancer survivors. Gynecol Oncol 100:479-486, 2006
10. Bye A, Trope C, Loge JH et al: Health-related quality of life and occurrence of intestinal side effects after pelvic radiotherapy--evaluation of long-term effects of diagnosis and treatment. Acta Oncol 39:173-180, 2000
11. Klee M, Machin D: Health-related quality of life of patients with endometrial cancer who are disease-free following external irradiation. Acta Oncol 40:816-824, 2001
12. Li C, Samsioe G, Iosif C: Quality of life in endometrial cancer survivors. Maturitas 31:227-236, 1999
13. Zhu L, Le T, Popkin D et al: Quality-of-life analysis in the management of endometrial cancer. Am J Obstet Gynecol 192:1388-1390, 2005

14. van de Poll-Franse LV, Mols F, Essink-Bot ML et al: Impact of External Beam Adjuvant Radiotherapy on Health-Related Quality of Life for Long-Term Survivors of Endometrial Adenocarcinoma: A Population-Based Study. Int J Radiat Oncol Biol Phys 2007
15. Dunberger G, Lind H, Steineck G et al: Self-reported symptoms of faecal incontinence among long-term gynaecological cancer survivors and population-based controls. Eur J Cancer 46:606-615, 2010
16. Ware JE, Jr., Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473-483, 1992
17. Aaronson NK, Muller M, Cohen PD et al: Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 51:1055-1068, 1998
18. Greimel E, Nordin A, Lanceley A, et al: Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24). Eur J Cancer 2010, doi:10.1016/j.ejca.2010.08.014 [Epub ahead of print]
19. Aaronson NK, van Andel G., EORTC Genito Urinary TractCancer Group: An international field of the reliability and validity of the QLQ-C30 and a disease-specific questionnaire module (QLQ-PR25) for assessing quality of life of patients with prostate cancer. European Organization for Research and Treatment of Cancer study protocol (15011). Brussels, 2002.
20. Greimel E, Bottomley A, Cull A et al: An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur J Cancer 39:1402-1408, 2003
21. Greimel ER, Kuljanic VK, Waldenstrom AC et al: The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. Cancer 107:1812-1822, 2006
22. Crespi CM, Ganz PA, Petersen L et al: Refinement and psychometric evaluation of the impact of cancer scale. J Natl Cancer Inst 100:1530-1541, 2008
23. Zebrack BJ, Ganz PA, Bernaards CA et al: Assessing the impact of cancer: development of a new instrument for long-term survivors. Psychooncology 15:407-421, 2006
24. Ringash J, O'Sullivan B, Bezjak A et al: Interpreting clinically significant changes in patient-reported outcomes. Cancer 110:196-202, 2007
25. Creutzberg CL, van Putten WL, Koper PC et al: Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol 89:201-209, 2003
26. J.Orton, P.Blake, and on behalf of ASTEC/EN.5 collaborators. Adjuvant external beam radiotherapy (EBRT) in the treatment of endometrial cancer: Results of the randomised MRC ASTEC and NCIC CTG EN.5 trial. J.Clin.Oncol. 25(18S). 20-6-2007.

27. Geinitz H, Zimmermann FB, Thamm R et al: Late rectal symptoms and quality of life after conformal radiation therapy for prostate cancer. Radiother Oncol 79:341-347, 2006
28. Hazewinkel MH, Sprangers MA, van d, V et al: Long-term cervical cancer survivors suffer from pelvic floor symptoms: a cross-sectional matched cohort study. Gynecol Oncol 117:281-286, 2010
29. Theis VS, Sripadam R, Ramani V et al: Chronic radiation enteritis. Clin Oncol (R Coll Radiol) 22:70-83, 2010
30. Yeoh EK, Bartholomeusz DL, Holloway RH et al: Disturbed Colonic Motility Contributes to Anorectal Symptoms and Dysfunction After Radiotherapy for Carcinoma of the Prostate. Int J Radiat Oncol Biol Phys 2010
31. Mundt AJ, Mell LK, Roeske JC: Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. Int J Radiat Oncol Biol Phys 56:1354-1360, 2003
32. Kerkhof EM, van der Put RW, Raaymakers BW et al: Intrafraction motion in patients with cervical cancer: The benefit of soft tissue registration using MRI. Radiother Oncol 93:115-121, 2009
33. Small W, Jr., Mell LK, Anderson P et al: Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys 71:428-434, 2008
34. Teunissen TA, van den Bosch WJ, van den Hoogen HJ et al: Prevalence of urinary, fecal and double incontinence in the elderly living at home. Int Urogynecol J Pelvic Floor Dysfunct 15:10-13, 2004
35. Tierney DK: Sexuality: a quality-of-life issue for cancer survivors. Semin Oncol Nurs 24:71-79, 2008
36. Lindau ST, Schumm LP, Laumann EO et al: A study of sexuality and health among older adults in the United States. N Engl J Med 357:762-774, 2007

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Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma

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Abstract

Purpose: To evaluate the very long-term results of the randomized Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 trial for patients with stage I endometrial carcinoma (EC), focusing on the role of prognostic factors for treatment selection and the long-term risk of second cancers.

Patients and methods: The PORTEC trial (1990-1997) included 714 patients with stage IC grade 1-2 or IB grade 2-3 EC. After surgery, patients were randomly allocated to external beam pelvic radiotherapy (EBRT) or no additional treatment (NAT). Analysis was by intention-to-treat.

Results: 426 patients were alive at the date of analysis. The median follow-up time was 13.3 years. The 15-year actuarial locoregional recurrence (LRR) rates were 6% for EBRT vs. 15.5% for NAT ($p<0.0001$). The 15-year overall survival (OS) was 52% vs 60% ($p=0.14$), and failure-free survival 50% vs 54% ($p=0.94$). For patients with high-intermediate risk criteria (HIR), 15-year OS was 41% vs. 48% ($p=0.51$), and 15-year EC-related death 14 vs 13%. Most LRR in the NAT group were vaginal recurrences (11% out of 15.5%). The 15-year rates of distant metastases were 9% vs 7% ($p=0.25$). Second primary cancers had been diagnosed over 15 years in 19% of all patients; 22% vs 16% for EBRT vs. NAT ($p=0.10$), with observed versus expected ratios of 1.6 (EBRT) and 1.2 (NAT) compared with a matched population (p=NS). Multivariate analysis confirmed the prognostic significance of grade 3 for LRR (hazard ratio [HR] 3.4, $p=0.0003$) and for EC death (HR 7.3, $p<0.0001$), of age >60 (HR 3.9, $p=0.002$ for LRR and HR 2.7, $p=0.01$ for EC death), and myometrial invasion >50% (HR 1.9, $p=0.03$ and HR 1.9, $p=0.02$).

Conclusions: The 15-year outcomes of PORTEC-1 confirm the relevance of high-intermediate risk criteria for treatment selection, and a trend for long-term risk of second cancers. EBRT should be avoided in patients with low- and intermediate-risk endometrial carcinoma.

Introduction

The Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 trial was one of four randomized trials that have established the role of radiotherapy (RT) in intermediate risk endometrial carcinoma (EC), showing that pelvic external-beam radiotherapy (EBRT) provides a highly significant improvement of local control, but without a survival advantage.[1-4] The majority (75%) of the locoregional (vaginal and/or pelvic) recurrences were located in the vagina, and treatment for vaginal recurrence was effective with 5-year survival of 70%, while outcomes after pelvic and distant relapse were poor.[5] EBRT was associated with 26% risk of side effects, mainly grade 1-2 gastro-intestinal (GI) toxicity.[6]

As a result of these trials, the indication for EBRT has become limited to patients with a relative high risk of recurrence. Risk factors have been identified: grade 3; age 60 years or older; and deep myometrial invasion. Patients with at least 2 of these 3 risk factors have been designated high-intermediate risk (HIR). Patients with HIR features have a 20% risk of locoregional recurrence (LRR) after no additional treatment (NAT), which is reduced to 5% with EBRT. For these HIR-patients the indication for radiotherapy has been maintained after PORTEC-1, and EBRT was abandoned for the 55% patients with stage I EC who were designated as low-intermediate risk (LIR).

In the Gynecology Oncology Group (GOG) 99 trial, which included patients with stage I-IIA EC after surgery which including lymphadenectomy (LA) with negative nodes, a similar HIR group was identified.[4] EBRT resulted in a hazard reduction of 58% both for LIR and HIR, but this reduction was clinically relevant only in the HIR group. The 4-year isolated local relapse rate was reduced from 13% to 5% in the HIR group.[4] These results were essentially the same as those from PORTEC-1, showing that both with and without LA, the risk factors grade 3, deep invasion, older age, and lymphovascular space invasion are associated with local recurrence.

The subsequent randomized PORTEC-2 trial for International Federation of Gynecology and Obstetrics (FIGO) 1988 stage I-IIA EC patients with HIR factors confirmed that EBRT could safely be substituted by vaginal brachytherapy (VBT), with less toxicity and better quality of life.[7,8] However, for high-risk EC -FIGO 2009[9] stages IB grade 3, II, III; or stages IB-III with serous/clear cell histology, EBRT continues to be the most effective adjuvant treatment for pelvic control.[10-12] The present analysis was done to evaluate very long-term outcomes of the PORTEC-1 trial, to investigate whether patients with HIR EC benefited more from EBRT than those without HIR factors, and to analyze the long-term risk of second cancers.

Patients and Methods

Patient selection and treatment

The PORTEC-1 trial was a multicenter trial accruing in 1990-1997. Details on patient evaluation and treatment have been described in previous publications.[3,6] Surgery consisted of total extrafascial hysterectomy and bilateral salpingo-oophorectomy without LA (only biopsy of any suspicious lymph nodes). Women of any age, World Health Organisation performance score 0-2, with endometrial adenocarcinoma stage I, grade 1 with deep (³50%) myometrial invasion, grade 2 with any invasion, or grade 3 with superficial (<50%) invasion were eligible. The protocol was approved by the Protocol Review Committee of the Dutch Cancer Society and by the Ethics Committees of the Daniel den Hoed Cancer Center and of the participating centers.

Radiation therapy

Pelvic EBRT was administered with a target volume that included the parametrial tissues, the proximal two-thirds of the vagina, and lymphatic drainage regions along the internal iliac vessels up to the promontory. The superior field border was at the L5-S1 disc. Total dose was 46 Gy in 2-Gy daily fractions. The PORTEC trial was done before 3-D conformal treatment planning techniques had been introduced. Radiation was delivered by AP-PA parallel opposed fields (30%), three-field (18%) or four-field techniques (52%) with calculation of the dose distribution on the central axis and specification at isocentre or midplane.[6]

Pathology review

Central pathology review was done after patient inclusion.[13] Histopathological slides of 567 patients (79%) were obtained. The diagnosis of endometrial carcinoma was confirmed in all patients. The histological grade was determined at review according to the FIGO 1988 grading criteria.[14,15] Systematic grading according to these criteria led to the assignment of grade 1 to significantly more tumors: 60% of the tumors were grade 1, 32% grade 2, and 8% were grade 3, in contrast to the initial assignment of 21% grade 1, 68% grade 2 and 11% grade 3. The outcomes in patients with grade 1 or 2 tumors were similar, in contrast to grade 3.[13] In the present analysis, histological grades determined at review have been used. In cases without pathology review the grade was assigned 'not done'. For determination of HIR and LIR groups, patients with review grade 'not done' were assigned grade 2.

Follow-up

Patients were followed in their regional hospitals until 7 years after treatment. The LRRs were confirmed by histology. LRR was defined as vaginal and/or pelvic recurrences. Distant failures included para-aortic lymph node metastases, abdominal relapses, liver, lung, and bone metastases and diffuse metastatic disease. For the present analysis, vital status of all patients considered to be alive and disease-free according to the trial database was checked with the Dutch Bureau for Genealogy and the Governmental local population administration (GBA). The analysis of long-term HRQL has been addressed in a separate publication.[16] The current analysis was done to evaluate prognostic factors, to establish the role of HIR factors for treatment selection, and to evaluate the long-term risk of second cancers after EBRT.

Statistical methods

The primary endpoints for the study were LRR and overall survival (OS). Secondary endpoints were morbidity and survival after relapse.

The analysis was by intention-to-treat. All randomized patients were kept in the analysis, including those who did not meet eligibility criteria (n=10) and those with protocol violations (n=31). The Kaplan-Meier method, log-rank test and Cox regression analysis were used for time-to-event analyses.[3,5]

Competing risk probabilities of failure were calculated with the following competing risks of first failure type: LRR, distant metastasis and death without relapse. If metastases were detected together with LRR, the failure type was metastases. Competing risk analysis was also applied to calculate probabilities of risk of death split by cause of death, and LRR split by type (vaginal or pelvic). Combined vaginal and pelvic recurrences were scored as pelvic recurrence.
The observed numbers of secondary cancers and deaths were compared with the expected numbers based on Dutch sex and age specific incidence rates of cancer and death[16] using the subject-years method.
Prognostic factors considered in the analysis were: age, depth of myometrial invasion, and (review) grade. Age (at randomization) was classified a priori in three groups (<60, 60-70 and >70 years). Differences between the treatment groups in risk of relapse or death were tested with the log-rank test without adjustment for prognostic factors, and with the likelihood ratio test in Cox regression analysis with adjustment. All reported p-values are based on two-sided tests with p-values <0.05 considered statistically significant.

Results

Outcomes

A total of 715 eligible patients with stage I EC were enrolled; 354 patients were randomly assigned to EBRT, and 361 to no additional treatment (NAT). One patient was excluded because all information was irretrievably missing. Thus, 714 patients were evaluated. The study groups were well balanced with regard to patient and tumor characteristics (Table 1).

Table 1: Patient characteristics after central pathology review

Characteristic	RT (n = 354)	NAT (n = 360)
	number of patients (%)	
Age (years)		
<60	93 (26)	108 (30)
60–70	136 (38)	134 (37)
>70	125 (35)	118 (33)
mean (sd)	66.3 (sd 9)	65.7 (sd 9)
range	41–85	43–90
Myometrial invasion		
< 50%	138 (39)	156 (43)
≥ 50%	216 (61)	204 (57)
Revised histologic grade		
1	198 (56)	197 (55)
2	49 (14)	39 (11)
3	32 (09)	54 (15)
nd*	75 (21)	70 (19)
Revised FIGO 1988 stage		
IB grade 1#	60 (17)	74 (21)
IB grade 2**	56 (16)	47 (13)
IB grade 3	22 (06)	35 (10)
IC grade 1	138 (39)	123 (34)
IC grade 2**	68 (19)	62 (17)
IC grade 3	10 (03)	19 (05)
Vascular space invasion		
present	22 (06)	19 (05)
HIR		
no	170 (48)	178 (49)
yes	184 (52)	182 (51)

*nd = no review grade; # at review ineligible; ** includes grade nd;
RT= radiotherapy; NAT= no additional treatment; sd= standard deviation;
HIR = high-intermediate risk

The present analysis was done on data frozen on March 1, 2009. Forty-eight patients were lost to follow-up (41 of whom were lost after >5 years' follow-up); they were included in the analysis and censored at the date of last follow-up. Median follow-up for patients alive was 13.3 years (range, 2.8-18.5 years). Table 2 shows the 15-year rates of LRR, metastases, OS and failure-free survival (FFS) by treatment group. The 15-year LRR rates were 5.8% in the RT group and 15.5% in the NAT group (hazard ratio [HR] for NAT 3.46; 95% CI 1.93-6.18;

log-rank test p< 0.0001). For comparison, the 5-year, 10-year and 15-year LLR rates were 4.2% vs. 13.7%; 4.6% vs. 14.3% and 5.8% vs. 15.5%. Among 50 LRR in the NAT arm, 37 (74%) were located in the vagina. The 15-year rate of distant metastases was similar in the treatment groups: 9.3% for EBRT and 7.1% for NAT (p=0.25). In both treatment arms some very late recurrences were diagnosed (Fig 1). All late recurrences were histologically confirmed, showing adenocarcinoma similar to the previous endometrial carcinoma. In one patient in the RT group, a large (6 cm) abdominal recurrence was diagnosed 16 years after treatment. She was started on hormonal therapy and is currently alive with partial remission. In two patients in the NAT group, vaginal recurrence and vaginal and pelvic recurrences were found after 9 and 14 years, respectively. These were treated with EBRT, and are currently without evidence of disease.

Table 2: Long-term outcomes at 15 years (actuarial probabilities) by treatment arm

Outcome	RT (n = 354)		NAT (n = 360)	
	Events	**15-yr % (SE)**	**Events**	**15-yr % (SE)**
Survival				
Alive	202	52% (3)	224	60% (3)
Death EC	37	11% (2)	30	8% (1)
Death other causes	115	38% (3)	106	31% (3)
Survival - HIR				
Alive	85	41% (4)	93	48% (4)
Death EC	25	14% (3)	24	13% (3)
Death other causes	74	45% (4)	65	39% (4)
Recurrence				
Vaginal	8	2.5% (0.6)	37	11.0% (1.3)
Pelvic	7	3.4% (1.6)	13	4.5% (1.4)
Distant	32	9.3% (1.6)	24	7.1% (1.4)
First failure				
No failure	198	50.1% (3.3)	203	54.4% (3.0)
Death NED	115	38.1% (3.2)	94	27.7% (3.0)
Vaginal recurrence	8	2.3% (0.8)	37	10.3% (1.6)
Pelvic recurrence	7	2.5% (1.0)	13	4.0% (1.1)
Distant recurrence	26	7.1% (1.4)	13	3.6% (1.0)
Second cancer				
Breast	11	4.8% (1.6)	18	6.6% (1.6)
GI	19	6.2% (1.4)	10	3.2% (1.0)
Other	25	10.6% (2.3)	14	6.0% (1.7)

RT= radiotherapy; NAT= no additional treatment; EC= endometrial carcinoma; NED=no evidence of disease; HIR= high-intermediate risk; GI = gastro-intestinal; se= standard error

A total of 288 patients had died: 67 due to EC (13 pelvic disease; 47 metastases; 1 related to primary treatment; 3 related to treatment of metastases; and 3 of unknown cause, but with previous diagnosis of relapse); and 221 due to other causes (51 second cancers; 165 intercurrent diseases; 5 unknown). The rates of death were compared with those of an age-matched population. Observed versus expected ratios were 1.14 for the total group; 1.22 in the EBRT group vs. 1.06 in the NAT group (p=N.S.).

In Fig. 2 the FFS rates by treatment group are shown for all patients and for those with HIR features. The FFS at 15 years was 50 vs. 54% (p=0.94), and among HIR patients FFS was nonsignificantly slightly higher in the EBRT group.

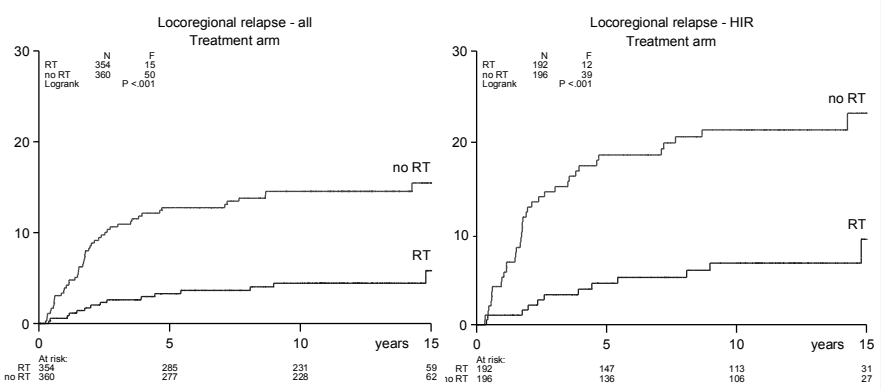

Fig. 1. Probability of locoregional (vaginal and/or pelvic) relapse for patients assigned to postoperative radiotherapy (RT) or no additional treatment (NAT) for the total group (left) and for patients with high-intermediate-risk (HIR) features (right).

Survival after recurrence

The 5- and 10-year survival rates after recurrence were significantly better in the NAT group: 48% (NAT) vs. 12% (EBRT) at 5 years, and 35% vs. 7% at 10 years ($p<0.01$). Survival rates after vaginal recurrence were 70% (NAT) vs. 38% (EBRT) at 5 years, and 51% vs. 25% at 10 years. Estimated 10-year survival rates for NAT vs EBRT were 18% vs 0% for pelvic relapse; and 8% vs 4% for distant relapse. Three patients with distant metastases were still alive and progression-free after 14, 12 and 10 years: two after surgical excision of a solitary pulmonary metastasis and a solitary omental metastasis, respectively; the third after salvage RT for vaginal recurrence and complete prolonged response on hormonal treatment of histologically verified pulmonary metastasis which had occurred 3 years after vaginal recurrence.

Second cancers

Second cancers were diagnosed in 97 patients, with 15-year rates of 22% in the EBRT group vs. 16% in the NAT group ($p=0.10$). The incidence rates were compared with those of an age-and sex-matched population: the observed vs. expected ratios were 1.40 for the total group; 1.62 for EBRT and 1.20 for NAT (p=N.S.).

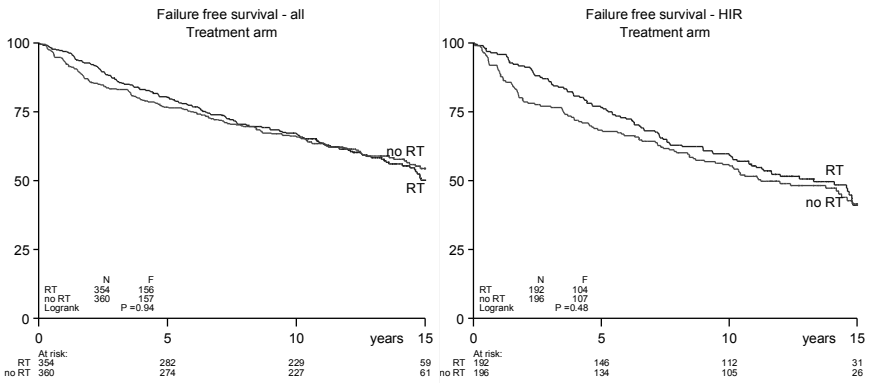

Fig. 2. Probability of failure-free survival for patients assigned to postoperative radiotherapy (RT) or no additional treatment (NAT) for the total group (left) and for patients with high-intermediate-risk (HIR) features (right).

Second cancer types were breast cancer (6% at 15 years), cancers of the GI tract (5%), and any other types (8%). The predominant cancer type among EBRT patients was GI cancer (6.2% vs. 3.2% among NAT patients), and breast cancer was most frequent in the NAT group (6.6% vs. 4.8% in the EBRT group). These differences did not reach statistical significance (p=0.10).

Prognostic factors

Table 3 shows multivariate analysis of prognostic factors for LRR and EC-related death. The HR for LRR, adjusted for major prognostic factors, were 3.46 for NAT compared to EBRT (p<0.0001), 3.35 for review grade 3 (p<0.001) and 1.66 for grade 2 (p=0.19) as compared to grade 1; and 3.90 for age ³60 years compared to <60 years (p=0.0017). Figure 3 shows OS split by prognostic factors. The risk of EC–related death was significantly higher for patients ³60 years and especially for patients with grade 3 tumors (HR 7.3, p<0.0001). After adjustment for age, grade and invasion there was no evidence of benefit of EBRT for OS or EC-specific survival.

Discussion

The recent publication of the results of the ASTEC trial included a meta-analysis of the ASTEC, GOG#99 and PORTEC-1 data, which excluded a survival benefit of EBRT in intermediate-risk endometrial cancer of more than 3%.2 Moreover, the results of previous meta-analyses suggested that EBRT may even be harmful for patients with features of low to intermediate risk, given that these patients have a low risk of recurrence after surgery alone, and EBRT adds toxicity and risks without improving survival.17,18 This was confirmed in the current analysis, with results showing a trend for lower OS after EBRT, whereas FFS curves overlapped. However, for patients with HIR features the OS rates were similar, and FFS was slightly (but nonsignificantly) higher after EBRT.

The abandonment of EBRT for patients with LIR features has been confirmed to be a correct decision. EBRT causes side effects6, and has been shown in our recent analysis to have a very long-term negative impact on HRQL.16 Moreover, we found a trend towards more second cancers among EBRT patients, especially cancers of the GI tract. EBRT can therefore not be justified in absence of survival benefit, and in presence of effective salvage RT for the very few LIR patients who develop locoregional recurrence. Although current sophisticated EBRT planning techniques (intensity-modulated RT) may be expected to have lower GI toxicity rates19, the irradiated volume in the lower pelvis remains large, and the long-term risks of pelvic floor dysfunction, GI symptoms, and second cancers cannot be disregarded.

For patients with HIR features the indication for RT was maintained, because their 5-year risk of LRR risk was 20%, which was considered sufficiently high to justify adjuvant treatment significantly improving local control. For these patients the subsequent PORTEC-2 trial showed that vaginal brachytherapy (VBT) was highly effective, with fewer side effects and better HRQL than after EBRT.8 Patients who received VBT did not have the increased bowel symptoms reported by EBRT patients, most notably diarrhea and urgency, resulting in higher need to remain close to a toilet.[7] As a result of the PORTEC-2 trial, patients with HIR EC are currently treated with VBT.

Table 3. Cox regression analysis

	Locoregional relapse			Death related to endometrial cancer		
Variable	**HR**	**95% CI**	***p*–value**	**HR**	**95% CI**	***p*–value**
NAT arm	3.46	1.93 - 6.18	<0.0001	0.71	0.43 - 1.16	0.17
Age ≥ 60	3.90	1.67 - 9.11	0.0017	2.66	1.26 - 5.61	0.010
Review grade 2	1.66	0.78 - 3.52	0.19	2.20	1.07 - 4.51	0.032
Review grade 3	3.35	1.75 - 6.41	0.0003	7.30	3.94 - 13.53	<0.0001
Invasion >50%	1.86	1.07 - 3.24	0.027	1.86	1.09 - 3.17	0.024
HIR patients						
NAT arm	3.31	1.73 - 6.35	0.0003	0.87	0.50 - 1.50	0.61
Review grade 2	1.53	0.62 - 3.79	0.35	1.93	0.81 - 4.60	0.14
Review grade 3	2.15	1.10 - 4.21	0.026	4.31	2.28 - 8.12	<0.0001

NAT= no additional treatment; CI= confidence interval; HIR= high-intermediate risk

External-beam RT has remained indicated only for the 15% of EC patients with high-risk features (grade 3 with deep invasion and/or lymph-vascular space invasion (LVSI), serous or clear cell histology) or advanced stages. Omitting EBRT for those patients has been shown to result in significantly lower pelvic control rates and may even affect survival.[10,12] The use of high-risk and HIR factors for decisions on adjuvant treatment underlines the critical importance of complete and reproducible pathology evaluation in the treatment of EC patients.

Adjuvant chemotherapy might be considered in view of the higher risk of distant metastases among patients with high-risk EC. Although two randomized trials comparing chemotherapy alone to pelvic EBRT alone did not show differences in OS, progression-free survival, or relapse rates20,21, the Nordic Society of Gynaecological Oncology / European Organisation fo Research and Treatment of Cancer (NSGO9501/EORTC55991) trial comparing EBRT alone with EBRT preceded or followed by chemotherapy showed a 7% increase in progression-free survival (p=0.03), and a trend for improved overall survival (p=0.08) in the combined arm.22 The current international randomized PORTEC-3 trial for patients with high-risk and advanced-stage EC investigates survival benefit, toxicities, and impact on quality of life of EBRT +chemotherapy compared

with EBRT alone. Both treatments are started early (2 cycles of cisplatin during EBRT and 4 cycles of carboplatin and paclitaxel after the completion of EBRT), which obviates the need to decide which treatment should be given first.23 Two current ongoing GOG trials (GOG 249 and 258) investigate the role of chemotherapy for early-stage HIR and high-risk EC (three cycles of carboplatin and paclitaxel and VBT vs. EBRT), and advanced stage EC (EBRT plus two cycles of cisplatin followed by four cycles carboplatin and paclitaxel vs. six cycles of carboplatin and paclitaxel).

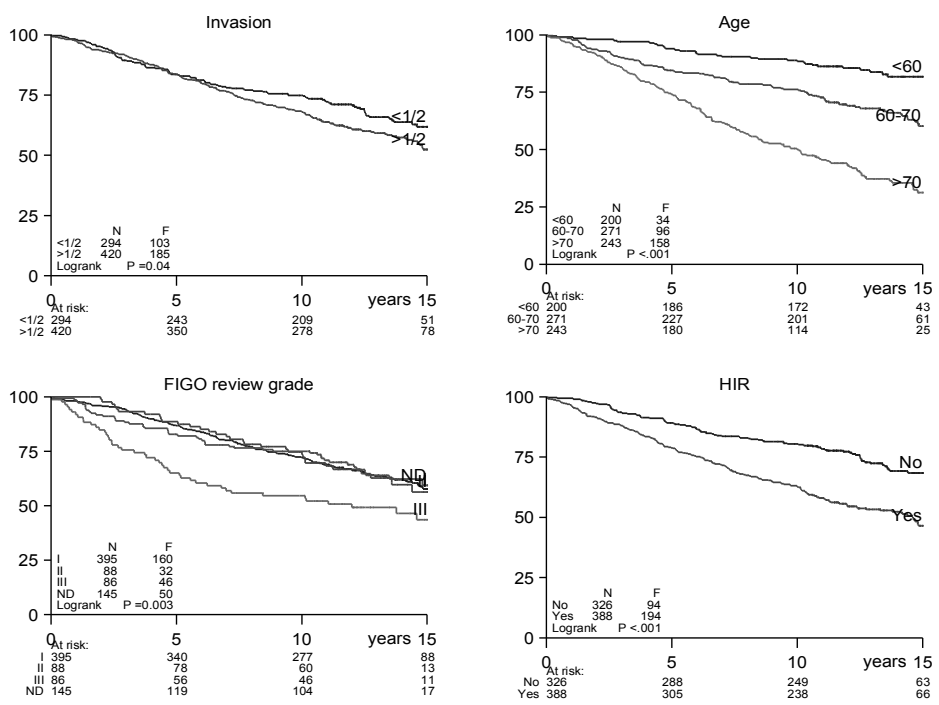

Fig. 3. Probability of overall survival according to prognostic factors: depth of myometrial invasion (<50% vs. $50%, top left), patient age (<60 vs. 60–70 vs. >70 years, top right), revised International Federation of Gynecology and Obstetrics (FIGO) Grade (1 vs. 2 vs. 3 vs. ND grade, bottom left), and presence vs. absence of high-intermediate-risk (HIR)features (bottom right).

PORTEC-1 and 2, GOG 99, and ASTEC trials2-4,8 have resulted in a significant reduction of the treatment burden for a large number of patients with endometrial carcinoma, abandoning EBRT for 85% of EC patients, and introducing VBT as adjuvant treatment for the 30% EC patients with HIR features. It should be noted that the favorable results in the control arm of PORTEC-1 and VBT arm of PORTEC-2 were obtained in the absence of LA, whereas only 30% of patients in the ASTEC trial underwent LA. These results were very similar to those of GOG 99[3], which required LA and only included patients who were node-negative. Two recent large randomized trials investigated the role of LA and did not find survival benefit or any differences in patterns and sites of relapse.[24,25] The Italian trial[24], which had median node count of 23 to 30 in the LA arm, showed identical rates of vaginal (2.6% for LA vs 2.4% for no-LA), lymph node recurrence (1.5% vs 1.6%) and intraperitoneal (3% vs 2.8%) relapse in both arms. The abandonment of EBRT for 85% of EC patients should thus not encourage increased use of LA to identify the 9% of patients with microscopic node metastases. This will not affect their survival and add morbidity: 18.6% vs. 8.8% risk of late complications for LA vs no LA, most notably 10.2% vs. 1.6% lymphedema.[24,26] Lymphedema has been shown to affect HRQL, and women with LA reported more clinically relevant edema symptoms (25.6% vs. 16.9%, $p<0.001$).[27] Powerful prognostic factors, especially grade 3 (with HR of 7.3 for EC death in the current analysis), and lymphovascular space invasion[28,29] are available at histologic examination and are associated with increased risk of distant spread. These factors can be used to select patients who might benefit from systemic treatments reaching areas that neither radiation nor the surgical knife can effectively treat.

In conclusion, 15-year results of the PORTEC-1 trial have confirmed the highly significant improvement of local control obtained by EBRT, but an absence of survival benefit. HIR features were shown to be useful for selection for RT (currently VBT). In view of the long-term negative impact of EBRT, the absence of survival benefit and presence of effective salvage treatment, the rationale for the abandonment of EBRT for intermediate-risk EC has been confirmed.

References

1. Aalders J, Abeler V, Kolstad P, et al: Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet.Gynecol. 56:419-427, 1980
2. Blake P, Swart AM, Orton J, et al: Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet 373:137-146, 2009
3. Creutzberg CL, van Putten WL, Koper PC, et al: Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 355:1404-1411, 2000
4. Keys HM, Roberts JA, Brunetto VL, et al: A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol.Oncol. 92:744-751, 2004
5. Creutzberg CL, van Putten WL, Koper PC, et al: Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol.Oncol. 89:201-209, 2003
6. Creutzberg CL, van Putten WL, Koper PC, et al: The morbidity of treatment for patients with Stage I endometrial cancer: results from a randomized trial. Int.J.Radiat. Oncol.Biol.Phys. 51:1246-1255, 2001
7. Nout RA, Putter H, JÅrgenliemk-Schulz IM, et al: Vaginal brachytherapy versus external beam pelvic radiotherapy for high-intermediate risk endometrial cancer: results of the randomized PORTEC-2 trial. LBA5503. J.Clin.Oncol. 26:1010s, 2008
8. Nout RA, Smit VT, Putter H, et al: Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 375:816-823, 2010
9. Pecorelli S: Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 105:103-4, 2009
10. Klopp AH, Jhingran A, Ramondetta L, et al: Node-positive adenocarcinoma of the endometrium: outcome and patterns of recurrence with and without external beam irradiation. Gynecol Oncol 115:6-11, 2009
11. Mariani A, Webb MJ, Keeney GL, et al: Stage IIIC endometrioid corpus cancer includes distinct subgroups. Gynecol Oncol 87:112-7, 2002
12. Mundt AJ, McBride R, Rotmensch J, et al: Significant pelvic recurrence in high-risk pathologic stage I--IV endometrial carcinoma patients after adjuvant chemotherapy alone: implications for adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 50:1145-53, 2001

13. Scholten AN, van Putten WL, Beerman H, et al: Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int.J.Radiat.Oncol.Biol.Phys. 63:834-838, 2005
14. Lax SF, Kurman RJ, Pizer ES, et al: A binary architectural grading system for uterine endometrial endometrioid carcinoma has superior reproducibility compared with FIGO grading and identifies subsets of advance-stage tumors with favorable and unfavorable prognosis. Am J Surg Pathol 24:1201-8, 2000
15. Blaustein's pathology of the female genital tract: Endometrial carcinoma. (ed 4th), Springer-Verlag, 1994 pp. 439-486
16. Nout RA, van de Poll-Franse LV, Lybeert ML, et al: Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. J.Clin.Oncol. 29:1692-1700, 2011
17. Johnson N, Cornes P: Survival and recurrent disease after postoperative radiotherapy for early endometrial cancer: systematic review and meta-analysis. BJOG 114:1313-20, 2007
18. Kong A, Johnson N, Cornes P, et al: Adjuvant radiotherapy for stage I endometrial cancer. Cochrane Database Syst Rev:CD003916, 2007
19. Mundt AJ, Mell LK, Roeske JC: Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. Int.J.Radiat.Oncol.Biol.Phys. 56:1354-1360, 2003
20. Maggi R, Lissoni A, Spina F, et al: Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. Br J Cancer 95:266-71, 2006
21. Susumu N, Sagae S, Udagawa Y, et al: Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. Gynecol Oncol 108:226-33, 2008
22. Hogberg T, Signorelli M, de Oliveira CF, et al: Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur.J.Cancer 46:2422-2431, 2010
23. Secord AA, Havrilesky LJ, O'Malley DM, et al: A multicenter evaluation of sequential multimodality therapy and clinical outcome for the treatment of advanced endometrial cancer. Gynecol Oncol 114:442-7, 2009
24. Benedetti PP, Basile S, Maneschi F, et al: Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J.Natl.Cancer Inst. 100:1707-1716, 2008
25. Kitchener H, Swart AM, Qian Q, et al: Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 373:125-136, 2009

26. May K, Bryant A, Dickinson HO, et al: Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev:CD007585, 2010
27. van de Poll-Franse LV, Pijnenborg JM, Boll D, et al: Health related quality of life and symptoms after pelvic lymphadenectomy or radiotherapy vs. no adjuvant regional treatment in early-stage endometrial carcinoma: a large population-based study. Gynecol Oncol 127:153-60, 2012
28. Briet JM, Hollema H, Reesink N, et al: Lymphvascular space involvement: an independent prognostic factor in endometrial cancer. Gynecol Oncol 96:799-804, 2005
29. Cohn DE, Horowitz NS, Mutch DG, et al: Should the presence of lymphvascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? Gynecol Oncol 87:243-6, 2002

6

Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data

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Abstract

Background: The PORTEC-2 trial showed efficacy and reduced side-effects of vaginal brachytherapy (VBT) compared with external beam pelvic radiotherapy (EBRT) for patients with high-intermediate risk endometrial cancer. The current analysis was done to evaluate long-term health related quality of life (HRQL), and compare HRQL of patients to an age-matched norm population.

Methods: Patients were randomly allocated to EBRT (n=214) or VBT (n=213). HRQL was assessed using EORTC QLQ-C30 and subscales from PR25 and OV28 (bladder, bowel, sexual symptoms); and compared to norm data.

Findings: Median follow-up was 65 months; 348 (81%) patients were evaluable for HRQL (EBRT n=166, VBT n=182). At baseline, patient functioning was at lowest level, increasing during and after radiotherapy to reach a plateau after 12 months, within range of scores of the norm population. VBT patients reported better social functioning (p=0.005) and lower symptom scores for diarrhoea, faecal leakage, need to stay close to a toilet, and limitation in daily activities due to bowel symptoms ($p \leq 0.001$), compared to EBRT. There were no differences in sexual functioning or symptoms between the treatment groups; however, sexual functioning was lower and sexual symptoms more frequent in both treatment groups compared to the norm population.

Interpretation: Patients who received EBRT reported clinically relevant higher levels of bowel symptoms and related limitations in daily activities with lower social functioning, 5 years after treatment. VBT provides a better HRQL, which remained similar to that of an age-matched norm population, except for sexual symptoms which were more frequent in both treatment groups.

Introduction

Endometrial carcinoma (EC) is the most common gynaecological malignancy among postmenopausal women in Western countries.[1] Surgery, consisting of total abdominal (or laparoscopic) hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) is the cornerstone of treatment.

Randomised trials have shown that pelvic external beam radiotherapy (EBRT) significantly reduced locoregional relapse, but without survival benefit, and at the cost of more (predominantly mild) gastro-intestinal toxicity.[2-6] Risk factors for locoregional recurrence were tumour grade 3, outer 50% myometrial invasion, age over 60 years, and lymph-vascular space invasion. Patients with these high-intermediate risk features had the largest benefit from EBRT (20% locoregional relapse without radiotherapy vs. 5% with EBRT). As most (75%) locoregional relapses were located in the vagina, the randomised PORTEC-2 trial was initiated to investigate if vaginal brachytherapy (VBT) would be equally effective for vaginal control, while reducing treatment toxicity and improving health related quality of life (HRQL) as compared to EBRT. Final results showed that VBT was indeed very effective in preventing vaginal recurrence with an estimated vaginal recurrence rate of 2% at 5 years, similar to the results obtained with EBRT.[7] Short-term HRQL results up to two years after treatment showed that rates of bowel symptoms such as diarrhoea and faecal leakage were significantly lower among women treated with VBT, with better social functioning compared to women treated with EBRT.[8] Symptom levels among VBT patients were very low. These results prompted adoption of VBT as standard of care for patients with high-intermediate risk EC in the Netherlands. Analysis of HRQL among PORTEC-1 patients 15 years after treatment showed that EBRT is associated with long-lasting symptoms impacting on patient functioning.[9] This finding underscores the importance of longitudinal HRQL analysis and reporting of late outcomes.

The current analysis was done to evaluate 5-year HRQL after EBRT and VBT of PORTEC-2 trial patients and compare their HRQL with that of an age-matched Dutch norm population.

Patients and Methods

Patient selection, treatment and study design of the PORTEC-2 trial

The multicenter PORTEC-2 trial randomly allocated EC patients with high-intermediate risk features to EBRT or VBT. Details on patient selection, treatment and HRQL have been described in previous publications.[7,8] In short, surgery consisted of TAH-BSO; clinically suspicious pelvic and/or periaortic lymph nodes were removed, but no routine lymphadenectomy was performed. FIGO 1988 staging was assigned on the basis of surgical and pathological findings.[10] Patients were eligible if they had one of the following combinations of age, grade and FIGO stage: (1) Age ≥60 years and stage 1C grade 1 or 2, or stage 1B grade 3; (2) stage 2A, any age (except grade 3 with outer 50% myometrial invasion). Written informed consent was obtained from all patients. The protocol was approved by the Dutch Cancer Society and the Ethics Committees of participating centres.

EBRT was given to a total dose of 46 Gy in 2 Gy daily fractions, 5 fractions/week. VBT was delivered to the upper half of the vagina using a vaginal cylinder. Brachytherapy dose schedules were used, equivalent to 45-50 Gy to the vaginal mucosa: high-dose-rate (90% of patients) 21 Gy at 5 mm depth in 3 fractions of 7 Gy over 2 weeks; low-dose-rate (10%) 30 Gy at 5 mm depth, in one session at 50-70 cGy/hr.

The primary endpoint was 5-year vaginal relapse (VR) as cumulative incidence, accounting for death as competing risk.[11] Secondary endpoints were HRQL, treatment related toxicity, pelvic lymph node and distant relapse and overall survival.

Quality-of-Life Assessment

Cancer-specific HRQL was measured with the EORTC (European Organization for Research and Treatment of Cancer) Core questionnaire (QLQ-C30 version 3.0).[12] No endometrial cancer-specific symptom questionnaire was available at the time; with approval of the EORTC Quality of Life Group, relevant subscales from existing published EORTC modules were combined into a symptom module (subscales for bowel and bladder symptoms from PR25 and subscale for sexual functioning and symptoms from OV28).[13,14] For all items Likert-type response scales were used, with response scales ranging from 1-4 points for all items except for items 29 and 30 (response scale 1-7). All subscales and individual item responses were linearly converted to 0 to 100 scales. A higher

score for a functional and global quality of life scale represents a better level of functioning. For the symptom scales and items, a higher score reflects a higher level of symptoms and decreased HRQL.

Baseline HRQL questionnaires were handed out at first consultation with the radiation oncologist 3-4 weeks after surgery, and were returned prior to RT. The end-of-treatment HRQL questionnaire was completed 2-4 weeks after RT. With consent, subsequent questionnaires were sent directly to the patient home address at 6, 12, 18, 24, 36, 48 and 60 months from randomization.

Patients were considered evaluable for the HRQL assessment if they had returned the baseline questionnaire and at least one of the follow-up questionnaires ('responders').

Statistical methods

All statistical analyses were performed using SPSS, version 17.0 (SPSS, Inc, Chicago, IL). Chi-square statistics or Fisher's exact test for categorical variables and *t* test for continuous variables were used to compare patient and tumour characteristics (significance p-value < 0.05).

HRQL analysis was done according to the guidelines provided by the EORTC Quality of life Group.[15] Descriptive median scores are presented in the tables. Baseline scores of both treatment groups were compared with a *t* test, or Armitage trend test for single items. In order to exclude a treatment effect on baseline scores, baseline forms completed later than the first day of radiotherapy were excluded for this comparison. To obtain estimates of the EORTC QLQ-C30, PR25 and OV28 subscales at each of the fixed time points, a linear mixed model was used with patient as random effect and time (categorical), randomization and their interaction as fixed effects. Single items were analyzed using (ordinal) logistic regression with random effects. The difference in HRQL between the two treatment groups was tested by Wald's test in the linear or ordinal logistic mixed model (*p*-randomization), excluding the baseline value. The same test was applied to look for significant changes of QOL scores over time (*p*-time), and score changes over time were compared between both treatment groups (*p*-time by randomization), including the baseline value. Age-matched Dutch norm population means[16] were compared with both treatment groups at each time point using the *t* test. To guard against false positive results due to multiple testing, a two sided *p*-value of 0.01 was considered statistically significant.

Recently published guidelines on the interpretation of clinical relevant changes of EORTC QLQ-C30 scores were applied (trivial, small, medium or large differences per scale).[17] For scales not included in the guideline, changes were evaluated according to Osoba, who found for the EORTC QLQ-C30 that patients valued a change of 5-10% as 'little', 10-20% as 'moderate' and more than 20% as 'very much' difference.[18]

Results

Study population and compliance

The PORTEC-2 trial accrued 427 patients between 2002 and 2006; 214 patients were allocated to EBRT and 213 to VBT. Baseline questionnaires and at least one follow-up questionnaire were received from 348 patients (81%), hereafter referred to as 'responders'. At the time of analysis (June 30th 2011), 268 of the 348 responders were alive, disease free and had reached the 5-year follow-up time point, of whom 206 (76%) returned the 5-year questionnaire (Web Appendix A). The median follow-up was 65 months (range 18-106 months), both for the whole trial population and for the responders.

All returned questionnaires were complete for all items of the QLQ-C30 in 82% of the responders, and for PR25 items in 92%; when allowing up to two missing items, these rates were 95% and 97%. In contrast, the sexual functioning subscale was complete for all items in 65%, and the sexual symptom subscale could be calculated for 81% of responders who were sexually active. The treatment groups did not differ with regard to questionnaire response rates and missing items. Although there were more EBRT patients among the non-responders (51 EBRT vs. 31 VBT patients p=0.02), patient characteristics were equally balanced between the EBRT and VBT group and between responders and non-responders (Table 1).

Tabel 1. Patient characteristics of responders and non-responders

	Responders (n=348)					Non-responders (n=79)		
	EBRT (n=166)		VBT (n=182)			No. of Patients	%	p-Value*
	No. of Patients	%	No. of Patients	%	p-Value‡			
Age, years								
mean	69.5		70.1		0.45	71,3		0.16
range	52-88		46-86			52-89		
<60 years	7	4.2	6	3.3	0.29	3	3.8	0.33
≥60 years	159	95.8	176	96.7		75	96.2	
FIGO-stage					0.73			0.99
1B	11	6.1	13	7.2		8	9.2	
1C	137	82.9	147	80.7		58	75	
2A	18	11	22	12.2		9	11.8	
Histologic Grade					0.83			0.42
Grade 1	77	46.4	89	48.9		36	46.1	
Grade 2	78	47	79	43.4		34	43.4	
Grade 3	11	6.6	14	7.7		9	10.5	
KPS					0.18			0.10
0	118	71.1	119	65.4		61	78.2	
1	47	28.3	59	32.4		16	20.5	
2	1	0.6	4	2.2		1	1.3	
Comorbidity								
IBD	2	1.2	2	1.1	0.93	2	2.6	0.34
Diabetes	19	11.4	31	17	0.14	12	15.4	0.82
Hypertension	61	37	63	34.8	0.68	26	33.3	0.68
Cardiovascular	38	23	42	23.1	0.99	18	23.4	0.95
Other	24	14.5	28	15.5	0.79	14	17.9	0.51

*EBRT: external beam radiotherapy; VBT: vaginal brachytherapy. KPS: Karnofski Performance Score; IBD: inflammatory bowel disease. FIGO: International Federation of Gynaecology and Obstetrics. ‡: p-Value for comparison EBRT vs. VBT. *: p-Value for comparison responders vs. non-responders.*

Patient functioning

For both treatment groups, global heath status and functioning scales were low at baseline and showed a medium to large improvement during radiotherapy and in the first 6 months, reaching a plateau within range of the scores of the norm population at 6-12 months (Fig. 1 and Table 2). Cognitive functioning remained unchanged from baseline onwards.

Patients treated with vaginal brachytherapy (VBT) reported significantly better social functioning scores, both at completion of VBT and during follow-up, than patients treated with EBRT. The maximum difference in mean social functioning scores between the groups was small (EBRT 83 vs. VBT 89, *p*-randomization = 0.005); this difference remained during the first year of follow-up.

Sexual activity and interest were lowest at baseline (i.e. after surgery), when 15% of the patients indicated that they were sexually active. There was a large increase of both interest and activity increased during the first 6 months to reach a plateau (39% active), without significant differences between the treatment groups (Fig. 1 and Table 2). For both EBRT and VBT patients however, mean sexual interest and activity scores were significantly lower than those of the age-matched norm-population. The maximum difference between EBRT or VBT patients and the norm population in mean sexual interest after 12 months was small and ranged between 6-10 points, and in sexual activity between 4-8 points. Among the patients who indicated they were active, 81% reported on their sexual symptoms. There were no significant differences in sexual symptoms between patients treated with EBRT or VBT. However, the norm population reported significantly less vaginal dryness and higher levels of sexual enjoyment.

Table 2. Patient functioning scores from EORTC QLQ-C30 and sexual functioning and symptom scores from OV-28.

	Questionnaire Time Points										p-Value		
				Month									Time by
	Baseline	p*	After RT	6	12	18	24	36	48	60	Time	Randomization	Randomization
EORTC QLQ-C30													
Global healt EBRT	69.3	0.55	73.4	76.3	76.1	77.2	76.9	77.5	75.9	76.7	**<0.001**	0.46	0.85
VBT	70.4		75.4	78.7	76.7	77.6	78.4	77.7	78.7	77.0			
Norm	75.4[F‡]		75.4	75.4	75.3	75.3	75.2	75.1	75.1	75.0			
Functional scales													
Physical func EBRT	72.0	0.42	76.5	79.3	78.4	78.8	77.8	76.4	76.6	75.2	**<0.001**	0.23	0.97
VBT	73.7		79.5	81.7	80.3	80.3	79.3	78.7	77.2	77,7			
Norm	82.0[F‡]		82.0[‡]	82.0	81.7	81.7	81.4	81.0	81.0	80.7[‡]			
Role functior EBRT	61.0	0.49	71.8	79.4	80.5	82.2	81.1	80.1	81.5	77.0	**<0.001**	0.27	0.26
VBT	59.1		76.8	83.3	81.6	83.3	81.5	83.3	81.6	81.5			
Norm	82.1[F‡]		82.1[F]	82.1	81.9	81.9	81.6	81.3	81.3	81.1			
Emotional fu EBRT	75.6	0.77	82.0	83.6	83.7	85.1	86.0	84.6	85.4	83.0	**<0.001**	0.39	0.58
VBT	76.3		83.5	84.4	84.3	87.0	85.3	87.6	85.8	87.2			
Norm	87.2[F‡]		87.2[F]	87.2	87.2	87.2	87.2	87.1	87.1	87.1			
Cognitive fur EBRT	84.3	0.26	86.0	85.9	86.5	86.4	86.1	86.1	87.6	83.4	0.28	0.24	0.66
VBT	86.7		87.5	89.2	88.7	88.8	87.4	87.9	87.0	87.8			
Norm	90.0[F]		90.0	90.0	89.9	89.9	89.8	89.7	89.7	89.6[F]			
Social functic EBRT	77.6	0.84	82.7	86.6	87.6	90.7	90.1	92.2	90.8	87.8	**<0.001**	**0.005**	0.09
VBT	78.1		89.1	92.6	93.1	93.7	91.9	93.7	92.2	92.4			
Norm	90.4[F‡]		90.4[F]	90.4	90.3	90.3	90.2	90.1	90.1	89.9			
EORTC OV-28													
Sexual functioning													
Sexual intere EBRT	8.0	0.08	10.0	14.4	13.6	15.0	14.2	14.9	14.2	14.0	**<0.001**	0.35	0.40
VBT	4.9		9.9	15.2	14.4	13.3	10.6	11.4	10.3	11.8			
Norm	22.3[F‡]		22.3[F‡]	22.3[F‡]	21.7[F‡]	21.7[F‡]	21.1[F‡]	20.5[‡]	20.5[‡]	20.0[‡]			
Sexual activit EBRT	5.4	0.07	9.6	12.9	12.8	12.1	11.1	12.8	10.8	8.3	**<0.001**	0.46	0.86
VBT	2.9		6.6	12.5	11.8	12.0	10.3	10.2	8.6	8.7			
Norm	18.2[F‡]		18.2[F‡]	18.2	17.6	17.6	17.1[‡]	16.5[‡]	16.5[‡]	15.9[F‡]			
Sexual symptoms													
extent was EBRT	46.8	0.02	40.6	44.3	49.1	48.9	46.5	47.8	49.2	50.7	0.068	0.27	0.025
sex VBT	21.0		45.5	47.2	42.8	49.9	40.6	36.1	42.7	42.4			
Norm	57.1[‡]		57.1[F]	57.1[F]	56.5[‡]	56.5	56.0[‡]	55.4[‡]	55.4	54.8			
Vaginal dryn EBRT	31.5	0.21	32.4	33.4	34.3	40.8	35.4	39.2	30.3	30.4	0.89	0.73	0.063
VBT	38.3		37.3	39.8	40.6	25.0	31.7	37.6	38.0	37.2			
Norm	19.4		19.4[‡]	19.4[‡]	19.8[F‡]	19.8[F]	20.3	20.7[F‡]	20.7	21.2[‡]			

*NOTE: for functioning scales a higher score indicates higher functioning, for symptom scales a higher score indicates more symptoms. EORTC: European Organisation of Research and Treatment of Cancer, QLQ-C30: Core Questionnaire, OV-28: ovarian cancer module. EBRT: external beam radiotherapy, VBT: vaginal brachytherapy, Norm: age matched Dutch population. After RT: after radiotherapy. * p-Value for baseline comparison, t test for comparing means, Armitage trend test for single items.F: p<0.01 for EBRT vs Norm; ‡: p<0.01 for VBT vs Norm.*

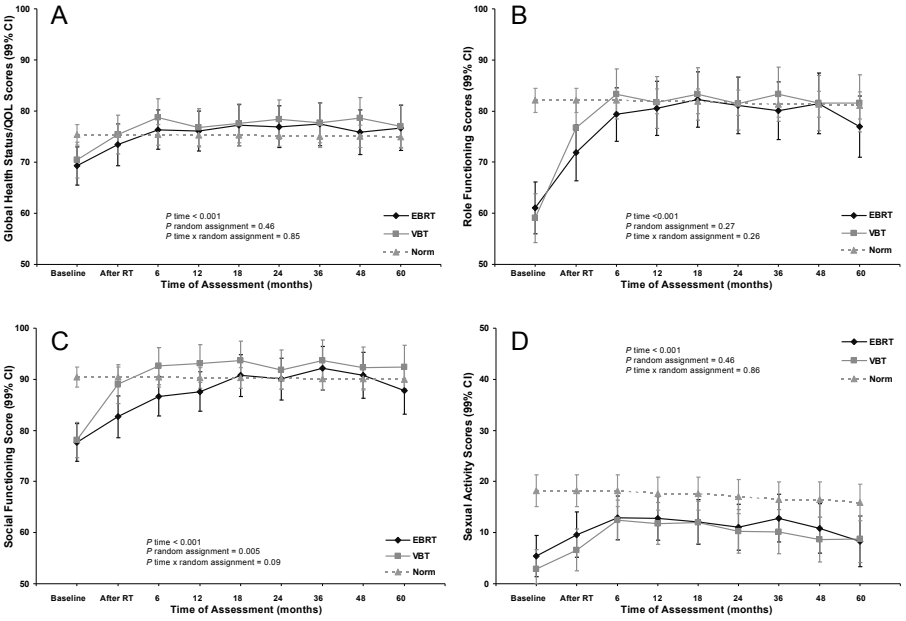

Fig. 1 - Patient functioning on subscales from European Organization for Research and Treatment of Cancer C30 questionnaire (EORTC QLQ-C30) and sexual activity score of the ovarian cancer questionnaire module (EORTC OV-28). A higher score indicates a higher level of functioning or activity. For EBRT and VBT error bars represent 99% Confidence Interval (CI), for Norm the error bars represent the 95% CI. The vertical axis is in the (A-C) upper-50% range; and (D) lower-50% range. VBT, vaginal brachytherapy; EBRT, external-beam radiotherapy; Norm, age-matched Dutch norm population; RT, radiation therapy.

Symptom scores

Patients treated with EBRT reported a large increase of diarrhoea scores at completion of RT, in contrast to VBT patients (31 EBRT vs. 10 VBT, *p*-randomization <0.001, Table 3 and Fig. 2). Diarrhoea scores of EBRT patients, although decreasing, remained at significantly higher levels throughout the 5-year follow-up period, whereas diarrhoea scores in the VBT group remained at baseline level (p-time < 0.001). There were no significant differences between diarrhoea scores of VBT patients and those of the norm population, whereas the diarrhoea scores of EBRT patients remained increased throughout 5 years after treatment. In addition, EBRT patients reported a little increase of faecal leakage 6 months after radiotherapy (11% EBRT vs. 3% VBT, *p*-randomization <0.001), remaining stable with further follow-up. Among the bowel symptoms, the item 'limitations of daily activities due to bowel problems' showed the largest difference between the treatment groups, in favour of VBT (23% EBRT vs. 7% VBT, *p*-randomization: <0.001). Moreover, EBRT patients reported a moderately increased need to remain close to the toilet.

Fatigue scores of both EBRT and VBT patients returned to levels in range with the norm-population after 6 months, while pain scores of both treatment groups were lower than those of the norm population.

Table 3. Symptom scores of EORTC QLQ-C30 and PR-25.

		Questionnaire Time Points										p-Value		
					Month									Time by
		Baseline	p*	After RT	6	12	18	24	36	48	60	Time	Randomization	Randomization
EORTC QLQ-C30														
Symptom scales														
Fatigue	EBRT	34.8	0.79	33.0	25.7	25.7	23.6	24.7	24.0	23.8	26.0	<0.001	0.061	0.54
	VBT	34.1		26.9	22.2	21.9	21.3	21.0	20.2	21.4	20.8			
	Norm	21.0[F‡]		21.0[F‡]	21.0	21.0	21.0	21.1	21.2	21.2	21.2			
Nausea and vomiting	EBRT	4.6	0.76	6.5	2.9	4.6	2.5	3.2	2.6	3.2	4.5	<0.001	0.017	0.23
	VBT	5.0		4.0	2.4	1.6	2.2	1.8	2.2	3.2	1.9			
	Norm	3.6		3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6			
Pain	EBRT	18.5	0.71	16.1	13.7	14.4	13.4	11.9	14.5	12.1	13.2	<0.001	0.38	0.75
	VBT	19.4		13.3	11.5	12.9	10.1	12.1	11.5	12.1	11.6			
	Norm	24.1		24.1[F‡]	24.1[F‡]	24.4[F‡]	24.4[F‡]	24.7[F‡]	25.0[F‡]	25.0[F‡]	25.4[F‡]			
Dyspnoea	EBRT	13.0	0.58	15.2	14.0	14.9	14.6	14.0	15.6	16.3	20.1	<0.001	0.72	0.032
	VBT	11.6		10.6	12.6	14.4	15.1	17.9	15.4	17.0	15.2			
	Norm	10.2		10.2	10.2	10.4	10.4	10.5[‡]	10.6	10.6[‡]	10.8[F]			
Insomnia	EBRT	27.4	0.60	23.5	22.4	21.7	21.4	22.8	24.4	24.0	26.1	0.001	0.17	0.93
	VBT	25.9		21.3	19.6	18.9	21.2	21.0	20.9	20.1	20.8			
	Norm	22.4		22.4	22.4	22.6	22.6	22.9	23.2	23.2	23.4			
Appetite loss	EBRT	13.7	0.22	16.8	9.7	8.9	5.6	7.5	7.8	6.3	8.4	<0.001	0.017	0.012
	VBT	10.6		7.7	3.7	4.5	5.1	6.5	5.3	5.5	5.6			
	Norm	5.0[F‡]		5.0[F]	5.0[F]	5.0	5.0	5,1	5,1	5,1	5,1			
Constipation	EBRT	13.4	0.78	7.6	6.4	6.2	6.9	9.0	8.3	8.9	10.7	<0.001	0.42	0.76
	VBT	12.9		6.7	6.2	8.0	7.5	7.7	7.0	9.3	7.1			
	Norm	8.7[F]		8.7	8.7	8.8	8.8	8.9	9.1	9.1	9.2			
Diarrhoea	EBRT	7.9	0.10	31.0	17.3	15.2	13.0	12.7	10.9	10.3	10.3	<0.001	<0.001	<0.001
	VBT	4.9		10.2	5.7	6.7	5.1	5.2	6.4	5.7	3.4			
	Norm	3.9		3.9[F‡]	3.9[F]	3.9[F]	3.9[F]	3.9[F]	3.9[F]	3.9[F]	3.9			
Financial difficulties	EBRT	2.0	0.02	5.4	3.5	2.3	3.2	2.2	1.1	2.0	3.7	0.002	0.95	0.14
	VBT	5.5		4.8	3.9	3.1	3.3	2.9	1.9	2.3	2.0			
	Norm	4.4		4.4	4.4	4.5	4.5	4.5	4.6[F]	4.6	4.6			

EORTC PR-25														
Urinary symptoms														
31. Frequency daytime	EBRT	33.2	0.26	39.0	30.9	32.9	31.4	29.1	34.1	31.6	31.3	<0.001	0.23	0.068
	VBT	36.5		37.3	28.7	25.3	26.9	28.7	28.6	27.5	28.5			
32. Frequency at night	EBRT	31.5	0.31	37.5	30.4	30.3	30.5	29.9	36.2	32.9	36.5	<0.001	0.24	0.033
	VBT	34,3		34.2	26.1	25.3	29.0	31.1	29.7	29.1	31.0			
33. Urinary urgency	EBRT	23.4	0.80	38.3	27.7	31.4	32.6	34.0	33.1	36.4	37.8	<0.001	0.21	0.022
	VBT	23.9		26.0	26.9	27.9	29.8	29.5	31.0	32.3	32.5			
34. Sleep deprivation due to US	EBRT	15.3	0.52	19.9	14.3	16.9	13.8	14.8	17.7	17.0	20.2	0.005	0.17	0.15
	VBT	16.3		13.6	10.2	14.1	12.6	14.3	15.1	15.0	14.0			
35. Need to remain close to toilet	EBRT	7.7	0.93	21.0	15.0	15.0	13.9	13.4	15.8	13.6	15.5	<0.001	0.001	0.001
	VBT	7.0		9.1	6.8	7.9	8.2	8.5	9.3	11.4	10.2			
36. Incontinence for urine	EBRT	11.4	0.76	17.7	13.7	17.3	17.1	17.9	21.5	20.4	24.2	<0.001	0.16	0.17
	VBT	10.6		13.3	14.2	15.7	14.9	16.8	17.3	18.9	17.1			
37. Dysuria	EBRT	5.3	0.14	8.6	3.4	2.9	1.5	2.6	1.3	1.2	2.0	<0,001	0.97	0.79
	VBT	7.9		9.5	3.7	3.5	1.5	1.7	1.6	1.0	1.4			
38. Limitation daily activities due to US	EBRT	3.6	0.82	8.4	6.0	6.7	5.6	8.9	9.8	7.2	10.2	<0.001	0.071	0.34
	VBT	3.0		6.0	4.4	3.9	4.7	6.1	4.4	4.6	5.9			
Bowel symptoms														
39. Limitation daily activities due to BS	EBRT	9.0	0.05	22.5	15.2	14.3	13.4	13.2	12.6	11.8	11.4	<0.001	<0.001	<0.001
	VBT	5.0		7.1	5.3	4.0	4.7	3.3	5.0	7.7	5.0			
40. Faecal leakage	EBRT	4.0	0.05	9.8	10.8	8.0	8.6	8.4	8.6	6.6	8.4	<0.001	<0.001	0.050
	VBT	1.5		4.7	2.5	2.5	3.6	2.0	3.0	4.8	2.9			
41. Rectal blood loss	EBRT	0.4	0.49	2.2	2.1	1.0	2.4	1.5	1.3	0.0	0.8	0.037	0.040	0.34
	VBT	0.2		1.2	0.9	0.9	0.3	0.8	0.4	0.6	0.0			
42. Bloated feeling	EBRT	15.5	0.84	16.4	16.3	14.6	12.8	10.6	12.7	11.7	12.1	<0.001	0.25	0.76
	VBT	15.5		14.2	13.0	10.6	10.4	9.6	9.5	13.2	9.6			

*NOTE: for functioning scales a higher score indicates higher functioning, for symptom scales a higher score indicates more symptoms. EORTC: European Organisation of Research and Treatment of Cancer, QLQ-C30: Core Questionnaire, PR-25: prostate cancer module. US: urinary symptoms, BS: bowel symptoms, EBRT: external beam radiotherapy, VBT: vaginal brachytherapy, Norm: age matched Dutch population. After RT: after radiotherapy. * p-Value for baseline comparison, t test for comparing means, Armitage trend test for single items. ǂ: p<0.01 for EBRT vs Norm; ǂ: p<0.01 for VBT vs Norm.*

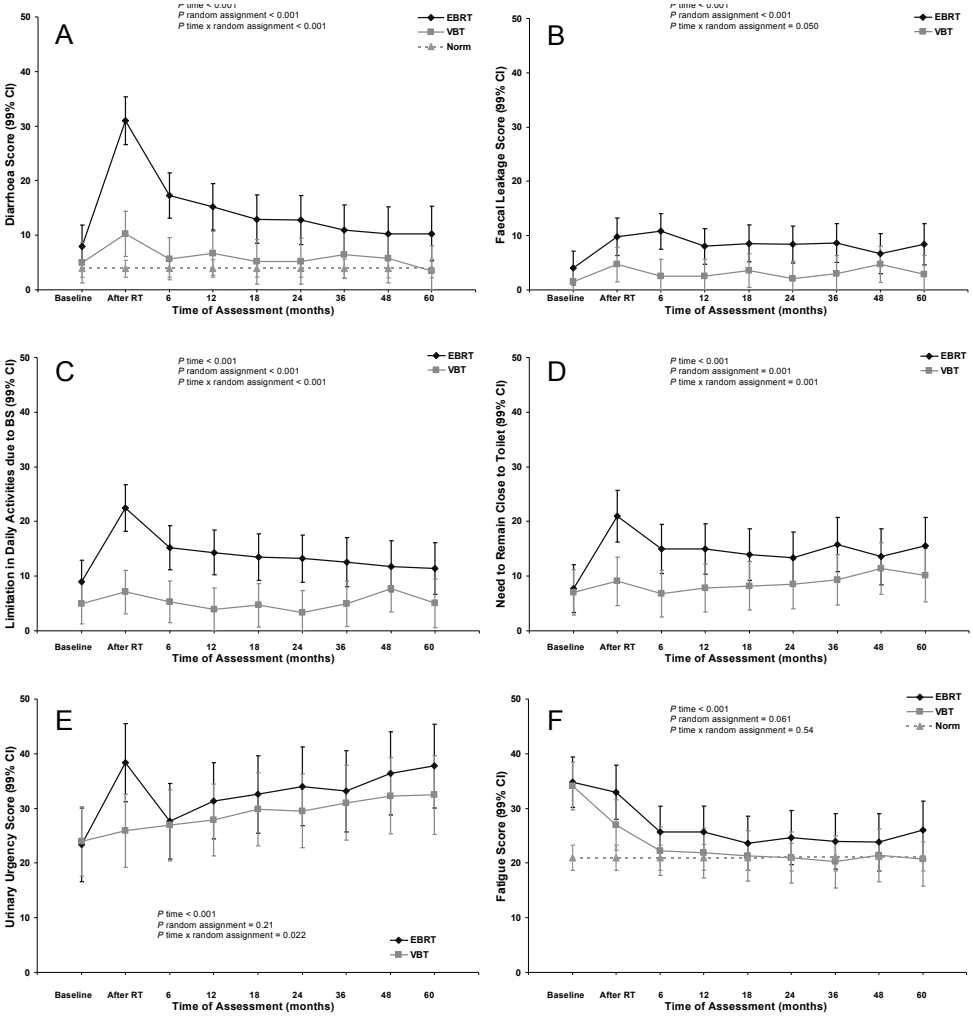

Fig. 2 - Single item symptom scores from European Organization for Research and Treatment of Cancer C30 questionnaire (EORTC QLQ-C30) and prostate cancer questionnaire module (EORTC PR-25). A higher score indicates a higher level of symptoms. For EBRT and VBT error bars represent 99% Confidence Interval (CI), for Norm the error bars represent the 95% CI. The vertical axis is in the (A-F) lower-50% range. VBT, vaginal brachytherapy; EBRT, external-beam radiotherapy; Norm, age-matched Dutch norm population; RT, radiation therapy.

Discussion

The current analysis of long-term HRQL of patients treated in the PORTEC-2 trial with a median follow-up of 65 months found a continuing long-term impact of EBRT on HRQL. Especially diarrhoea and faecal leakage were increased after EBRT, leading to a higher need to remain close to a toilet; more limitations of daily activities due to bowel problems; and a lower level of social functioning. HRQL of patients treated with VBT remained very similar to that of a healthy age-matched norm population. In contrast, sexual aspects of HRQL after treatment for endometrial cancer were lower than that of the norm population, irrespective of the type of adjuvant radiotherapy.[16]

Diarrhoea scores of VBT patients remained at the norm population level, while the scores of EBRT patients remained significantly increased up to 5 years after treatment. Furthermore, scores on the global health status scale and functioning scales of both EBRT and VBT patients were significantly lower than norm data at baseline (after surgery), and recovered in the first 6 months to reach a plateau within range of the age-matched norm population. A similar pattern was found for fatigue scores. These results indicate that for most women the stressful period of diagnosis and treatment for endometrial cancer has a clear but transient influence on their general functioning.

The persisting increased rates of bowel symptoms after EBRT are consistent with the increased gastrointestinal toxicity rates after EBRT found in randomised trials and retrospective studies on long-term morbidity after pelvic radiotherapy.[19-21] In the HRQL analysis of PORTEC-1 trial survivors 15 years after treatment, increased bowel symptom rates were reported by EBRT patients as compared to those treated with surgery alone, indicating the persistence of these symptoms over time.[9]

Reported late side effects of vaginal brachytherapy include atrophic changes in the vaginal mucosa leading to vaginal dryness, painful intercourse, and vaginal fibrosis leading to tightening and/or shortening. Analysis of vaginal mucosal changes as assessed at gynaecological examinations showed an increase of grade 1 and 2 mucosal atrophy from 6 months onwards (at 3 years 17% after EBRT vs. 35% after VBT).[7] Despite the increased rate of grade 1-2 mucosal atrophy, there were no significant differences in sexual functioning and sexual symptoms between patients treated with EBRT or VBT. However, sexual functioning (activity and interest) scores of both EBRT and VBT were

lower than those of the age-matched norm-population, and sexual symptoms were increased. The rates of sexual activity and symptom scores reported by PORTEC-2 trial patients were similar to the long-term scores of PORTEC-1 trial survivors, also those treated with surgery alone, suggesting an impact of cancer diagnosis and treatment on sexual aspects of HRQL.[9] Limitations to any conclusion are the low rate of sexual activity in this elderly population, and the lower completion rate of the sexual functioning questions.
A striking finding of the 15-year HRQL analysis of the PORTEC-1 trial was the increase rate of urinary urgency and incontinence. In the current analysis of 5-year HRQL in the PORTEC-2 trial, there were no differences in urinary symptoms between the groups. However, from 12 months onwards a trend towards higher incontinence and urgency scores after EBRT seemed to emerge. Possibly, these late urinary symptoms develop as a result of added long-term impact of EBRT upon normal ageing changes of the pelvic floor muscles. A future analysis of very long-term HRQL in PORTEC-2 will include questions on incontinence pad usage. Future studies should investigate preventive measures to maintain pelvic floor functioning to diminish the added effect of RT on normal ageing.

In conclusion, up to 5 years after treatment, EBRT has a clinically relevant, bowel symptom-related negative impact on HRQL, with limitation of daily activities. Global health status and functioning scores of all patients returned to levels of an age-matched Dutch norm population after 6-12 months, indicating that for most women diagnosis and treatment for endometrial cancer has a clear but transient influence on their general functioning. Compared to the norm population, EC patients reported lower levels of sexual functioning and more sexual symptoms after treatment, without differences between patients who received EBRT or VBT.

References

1. Bray, F., Loos, A. H., Oostindier, M., and Weiderpass, E.: Geographic and temporal variations in cancer of the corpus uteri: incidence and mortality in pre- and postmenopausal women in Europe. Int J Cancer, 117: 123, 2005.
2. Aalders, J., Abeler, V., Kolstad, P., and Onsrud, M.: Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol, 56: 419, 1980.
3. Blake, P., Swart, A. M., Orton, J., Kitchener, H., Whelan, T., Lukka, H. et al.: Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet, 373: 137, 2009.
4. Creutzberg, C. L., van Putten, W. L., Koper, P. C., Lybeert, M. L., Jobsen, J. J., Warlam-Rodenhuis, C. C. et al.: Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet, 355: 1404, 2000.
5. Creutzberg, C. L., van Putten, W. L., Koper, P. C., Lybeert, M. L., Jobsen, J. J., Warlam-Rodenhuis, C. C. et al.: The morbidity of treatment for patients with Stage I endometrial cancer: results from a randomized trial. Int J Radiat Oncol Biol Phys, 51: 1246, 2001.
6. Keys, H. M., Roberts, J. A., Brunetto, V. L., Zaino, R. J., Spirtos, N. M., Bloss, J. D. et al.: A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol, 92: 744, 2004.
7. Nout, R. A., Smit, V. T., Putter, H., Jurgenliemk-Schulz, I. M., Jobsen, J. J., Lutgens, L. C. et al.: Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet, 375: 816, 2010.
8. Nout, R. A., Putter, H., Jurgenliemk-Schulz, I. M., Jobsen, J. J., Lutgens, L. C., van der Steen-Banasik EM et al.: Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol, 27: 3547, 2009.
9. Nout, R. A., van de Poll-Franse LV, Lybeert, M. L., Warlam-Rodenhuis, C. C., Jobsen, J. J., Mens, J. W. et al.: Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. J Clin Oncol, 29: 1692, 2011.
10. Shepherd, J. H.: Revised FIGO staging for gynaecological cancer. Br J Obstet Gynaecol, 96: 889, 1989.

11. Putter, H., Fiocco, M., and Geskus, R. B.: Tutorial in biostatistics: competing risks and multi-state models. Stat Med, 26**:** 2389, 2007.
12. Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J. et al.: The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst, 85**:** 365, 1993.
13. Aaronson, N. K., van Andel G., and EORTC Genito Urinary TractCancer Group: An international field of the reliability and validity of the QLQ-C30 and a disease-specific questionnaire module (QLQ-PR25) for assessing quality of life of patients with prostate cancer. European Organization for Research and Treatment of Cancer study protocol (15011). Brussels: 2002.
14. Greimel, E., Bottomley, A., Cull, A., Waldenstrom, A. C., Arraras, J., Chauvenet, L. et al.: An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur J Cancer, 39**:** 1402, 2003.
15. Fayers PM, Aaronson NK, Bjordal K, Curran D, Groenvold M, and on behalf of the EORTC Quality of Life Study Group.: EORTC QLQ-C30 Scoring Manual (Second edition). Brussels: EORTC, 1999.
16. van de Poll-Franse LV, Mols, F., Gundy, C. M., Creutzberg, C. L., Nout, R. A., Verdonck-de, L., I et al.: Normative data for the EORTC QLQ-C30 and EORTC-sexuality items in the general Dutch population. Eur J Cancer, 47**:** 667, 2011.
17. Cocks, K., King, M. T., Velikova, G., Martyn St-James, M., Fayers, P. M., and Brown, J. M.: Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol, 29**:** 89, 2011.
18. soba, D., Rodrigues, G., Myles, J., Zee, B., and Pater, J.: Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol, 16**:** 139, 1998.
19. Dunberger, G., Lind, H., Steineck, G., Waldenstrom, A. C., Nyberg, T., al-Abany, M. et al.: Self-reported symptoms of faecal incontinence among long-term gynaecological cancer survivors and population-based controls. Eur J Cancer, 46**:** 606, 2010.
20. Geinitz, H., Zimmermann, F. B., Thamm, R., Erber, C., Muller, T., Keller, M. et al.: Late rectal symptoms and quality of life after conformal radiation therapy for prostate cancer. Radiother Oncol, 79**:** 341, 2006.
21. Hazewinkel, M. H., Sprangers, M. A., van, d., V, van, d., V, Stalpers, L. J., Burger, M. P. et al.: Long-term cervical cancer survivors suffer from pelvic floor symptoms: a cross-sectional matched cohort study. Gynecol Oncol, 117**:** 281, 2010.

7

Improved risk assessment of endometrial cancer by combined analysis of MSI, PI3K-AKT, Wnt/ß-catenin and P53 pathway activation

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Abstract

Objective: To investigate if analysis of genetic alterations in the main pathways involved in endometrioid type carcinogenesis (PI3K-AKT, Wnt/β-catenin, P53-activation and MSI) improves the current risk assessment based on clinicopathological factors.

Methods: Formalin fixed paraffin embedded (FFPE) primary tumor samples of 65 patients with FIGO-stage I endometrioid type endometrial cancer (EEC) were selected from the randomized PORTEC-2 trial. Tumors were stained by immunohistochemistry for P53, PTEN and ß-catenin. Tumor DNA was isolated for sequence analysis of *TP53* (exons 4 to 8), hotspot mutation analysis of *KRAS* (exon 1) and *PI3K* (exon 9 and 20) and microsatellite-instability (MSI) analysis including *MLH1* promotor-methylation status. Univariate and multivariate analyses for disease-free survival (DFS) using Cox regression models were performed.

Results: P53 status (HR 6.7, 95%CI 1.75 – 26.0, p=0.006) and MSI were the strongest single genetic prognostic factors for decreased DFS, while high PI3K-AKT pathway activation showed a trend and ß-catenin was not prognostic. The combination of multiple activated pathways was the most powerful prognostic factor for decreased DFS (HR 5.0; 95%CI 1.59 – 15.6 p=0.006). Multiple pathway activation, found in 8% of patients, was strongly associated with aggressive clinical course. In contrast, 40% of patients had no alterations in the investigated pathways and had a very low risk of disease progression.

Conclusions: Activation of multiple oncogenic pathways in EEC was the most powerful prognostic factor for decreased DFS, resulting in an individual risk assessment superior to the current approach based on clinicopathological factors.

Introduction

Endometrial cancer (EC) is the most common gynecological cancer in Western countries.[1] Surgery alone (hysterectomy and bilateral salpingo-oophorectomy) is a curative treatment for the majority of patients.[2,3]

This study focuses on type 1 EC (EEC), the most frequent subtype (80-85%), characterized by endometrioid morphology. The remaining 15-20% are type 2 cancers with a non-endometrioid morphology (NEEC), mostly serous or clear cell cancers having a far more aggressive clinical behavior than type 1 cancers. Adjuvant treatment for EEC has become increasingly tailored to clinicopathological risk factors.[4] In low-risk EEC patients adjuvant treatment is not indicated, while high-risk EEC patients receive adjuvant radiotherapy and/or chemotherapy. The (high)intermediate risk category of EEC patients has at least two high-intermediate risk (HIR) features; advanced age, grade 3, deep invasion, and LVSI.[5,6] The PORTEC-2 trial, in which HIR patients were randomly allocated to external beam radiotherapy or vaginal brachytherapy, concluded that vaginal brachytherapy is an effective therapy to prevent local recurrence with <2% vaginal recurrence at 5 years and 8% distant metastasis.[7] Despite tailoring adjuvant therapy to clinicopathological factors, considerable over- and undertreatment still exists. Approximately 7 HIR patients need to receive brachytherapy to prevent 1 vaginal recurrence.

The signaling pathways currently known to drive EEC development are activation of the phosphatidylinositol 3-kinase (PI3K)-AKT pathway, Wnt/β-catenin-signaling, microsatellite-instability (MSI) and, although typically described in NEEC, mutational activation of TP53.[8-10] The PI3K-AKT pathway can be deregulated by many different mechanisms, including inactivation of PTEN or mutations in PI3K and KRAS.[11] A recently investigated marker of PI3K-AKT pathway activation, Stathmin (STMN1), was shown to have independent prognostic capacity and may reflect the degree of PI3K-AKT pathway activation.[12] As in other cancers, endometrial carcinogenesis is likely to be the result of a complex interaction of pathway alterations. Concomitant PI3K-AKT and P53 alterations were found to be associated with poor prognosis.[13] Most studies

have however focused on single oncogenic pathway alterations in EEC and were performed in a heterogenic population containing both EEC and NEEC and both early and advanced FIGO stage tumors.

The aim of the present study was to investigate whether combined analysis of genetic alterations in the main pathways involved in endometrioid type carcinogenesis can help to improve the current clinicopathological risk assessment of patients with EEC.

Methods

Patient and tissue selection

The current analysis was undertaken in a sample size of 65 EEC patients selected from the PORTEC-2 trial population (427 participants). Written informed consent was obtained from all patients and included consent for collection of a tumor sample. The trial protocol was approved by the Dutch Cancer Society (CKTO 2001-04) and the ethics committees of all participating centers. Eligible trial patients had EEC with HIR factors based on the original pathology report of the treatment center. At central pathology review some EC were diagnosed to have low-risk (LR, 6%) or high-risk (HR, 8%) features.[7] In order to detect a trend in the incidence of alterations in oncogenic pathways in the LR, HIR and HR risk groups, all patients who were found to have LR (N=23) or HR features (N=16) at review and of whom tissue samples were available, were included in the current selection. In addition, sufficient disease-related events were required to correlate the pathway alterations with disease recurrence. For this purpose, from the subgroup of patients with HIR features, with grade 1-2 tumors with deep (>50%) myometrial invasion, confirmed after review (true-HIR, 366 patients) tissue samples of 26 patients were selected with the aim to include 50% of patients with disease recurrence during follow-up.

Formalin fixed paraffin-embedded (FFPE) blocks containing representative tumor were selected. Hematoxylin-eosin stained slides were viewed by an experienced gynecopathologist (V.S.), in order to select an area of tumor tissue containing at least 70% tumor cells. From this area two to three 0.6 mm cores

were extracted and used to isolate tumor DNA after proteinase K digestion. For the immunohistochemistry (P53, β-catenin, PTEN, Stathmin) procedures 4µm whole slide sections were used.

Mutational analysis

All samples were analyzed using a custom made panel of hydrolysis probe assays, designed to detect hotspot mutations in PIK3CA (*PI3K)* and *KRAS*.[14] The hotspot mutations investigated for *PI3K* were exon 9, c.1624G>A; p.E542K and c.1633G>A; p.E545K and in exon 20 the c.3140A>G; p.H1047R and for *KRAS* exon 1, c.34G>A; p.G12S, c.34G>C; p.G12R, c.34G>T; p.G12C, c.35G>A; p.G12D, c.35G>C; p.G12A, c.35G>T; p.G12V and c.38G>A; p.G13D. Real time qPCR was performed by allelic discrimination using primers and probes designed and ordered by Applied Biosystems (Applied Biosystems, Nieuwerkerk aan de IJssel, the Netherlands).

Microsatellite instability (MSI) and Methylation-specific PCR

The microsatellite status of each tumor was determined using the Promega MSI analysis system (version 1.2, Promega, Madison, WI, US) , following the recommendation of the National Cancer Institute/ICG-HNPCC.[15] Tumors were classified as microsatellite instable (MSI) when two or more markers showed an instable pattern. The MSI tumors were selected for further testing for methylation status of the 5' regulatory region of MLH1, using methylation-specific PCR (MSP), with primers that have been previously described.[16]

TP53 Mutation Analysis

Primers were designed to amplify exons 4-8 of *TP53* by PCR. *TP53* primers were designed to avoid amplification of a pseudogene, and have been described previously.[17] Sanger sequencing was performed on purified PCR products (Macrogen, Amsterdam, the Netherlands). Sequences were analyzed with Mutation Surveyor™ DNA variant analysis software (version 3.97 Softgenetics). A mutation was only accepted once it was identified in both forward and reverse strands.

Immunohistochemistry

Slides were deparafinated in xylene, rehydrated though a graded ethanol series, and washed with phosphate-buffered saline. Antigen retrieval was achieved by microwave oven treatment for 10 min in 10mmol/L citrate buffer, pH6.0 (ß-catenin in 10 mmol/L Tris-EDTA, pH9.0). Sections were incubated overnight with monoclonal p53 antibody (clone D0-7, 1:1000 dilution; NeoMarkers), polyclonal Stathmin antibody (3352, 1:100 dilution, Cell Signaling), PTEN (clone 6.H2.1, 1:200 dilution; DAKO), ß-catenin (cat. 610154; 1:1600; BD Transduction) and monoclonal MLH-1 (clone ES05, 1:200 dilution; DAKO). The sections were incubated and stained with a secondary antibody (Poly-HRP-GAM/R/R; DPV0110HRP; ImmunoLogic). Diaminobenzidine tetrahydrocholoride was used as a chromogen for all antibodies. The slides were counterstained with hematoxylin.

Evaluation of staining

Slides were evaluated by two pathologists (T.B. and V.S), blinded for patient characteristics and outcome. Evaluations were done independently, and discrepancies were resolved at simultaneous viewing. P53 was scored positive if >50% of the tumor cells showed strong positive nuclear staining, or when discrete geographical patterns showed >50% tumor cell positivity.[18] Activated Wnt-signaling was defined as nuclear staining of ß-catenin. For Stathmin and PTEN a semi quantitative grading system incorporating staining intensity (score 0-3) and area of tumor with positive staining was used, as described by Trovik et. al.[19]: 0, no staining; 1, <10%; 2, 10-50%, and 3, >50% of tumor cells. Staining index was calculated as the product of staining intensity and staining area, range 0-9. Values defined by the upper quartile for the data set were considered positive.

Statistics

The distribution of patient and tumor characteristics of the different risk groups was tested for significance using the Chi-square test for categorical variables and the student T-test for continuous variables. Disease free survival (DFS) was defined as the time between date of randomization and date of

disease recurrence or death from any cause; all other patients were censored at the date of last follow-up. DFS was calculated with the Kaplan Meier method including Log rank test. Multivariate analysis of prognostic factors for disease free survival was performed using Cox regression models. All variables with a univariate Log rank p-value less than 0.1 were included in the model. SPSS software version 17.0 was used for statistical analysis.

Results

Patient characteristics

Patient characteristics are shown in Table 1. Median follow-up was 88 months (range 4 – 106 months) and was not significantly different from the main trial population (p=0.29).

Despite the disease free survival (DFS) rate being lower in the true-HIR population (N=26) due to selection of patients with recurrent disease, DFS in the total population (N=65) did not differ significantly from that of the original trial population (N=427) (Appendix 1). In total 15 of 65 (23.1%) patients recurred during follow-up, while 12 of 26 (46.2%) true-HIR patients recurred during follow-up (Table 1).

In univariate analysis both age (p=0.03) and deep myometrial invasion (p=0.02) were prognostic factors for decreased DFS, and were included in the subsequent Cox regression analysis, in contrary to grade (p=0.26) and lymph vascular invasion (p=0.15).

Table 1. Patient, tumor and treatment characteristics of endometrioid type tumors.

	Low Risk		High-intermediate Risk		High Risk		Total		
	No.	%	No.	%	No.	%	No.	%	p-value*
Total	23	35.4	26	40.0	16	24.6	65	100	
Age at Diagnosis									
Mean	64.7		70.1		68.8		67.9		**0.04**
Range	51.6 - 84.6		56.0 - 82.0		60.7 - 82.7		51.6 - 84.6		
Myometrial Invasion									
<50%	23	100	0	0	0	0	23	35.4	**<0.001**
>50%	0	0	26	61.9	16	38.1	42	64.6	
Grade									
1	21	55.3	17	44.7	0	0	38	58.5	**<0.001**
2	2	18.2	9	81.8	0	0	11	16.9	
3	0	0	0	0	16	100	16	24.6	
Lymph Vascular Invasion									
Abstent	21	39.6	22	41.5	10	18.9	53	81.5	*0.07*
Present	2	16.7	4	33.3	6	50.0	12	18.5	
Treatment arm									
EBRT	10	32.3	13	41.9	8	25.8	31	47.7	0.88
VBT	13	38.2	13	38.2	8	23.5	34	52.3	
Site of First Recurrence									
No Recurrence	22	44.0	14	28.0	14	28.0	50	76.9	**0.01**
Pelvic Lymph Node Recurrence	0	0	1	100	0	0	1	1.5	
Distant Metastasis	1	7.1	11	78.6	2	14.3	14	21.5	

EBRT: external beam radiotherapy; VBT: vaginal brachytherapy.
**p-value by χ2 method, p-values <0.05 in bold and between 0.05 and 0.10 in italic.*

PI3K-AKT pathway activation

PI3K mutations were found in 7 tumors (11%) of which 5 had a mutation in exon 20 (H1047R). KRAS mutations in exon 1 were found in 14 tumors (22%) of which 11 were located at position 35. Loss of PTEN expression was found in 45% of the tumors. Both PI3K and KRAS mutation status alone were not predictive for decreased DFS, while loss of PTEN expression showed a trend for decreased DFS (Table 2).

PI3K-AKT pathway activation was classified as high when two or more altered genetic factors (PI3K and KRAS mutation status and loss of PTEN) were found (12/65 tumors, 19%), moderate in case of one altered genetic factor and no pathway activation if none of the factors were altered (26/65 tumors, 40%). High PI3K-AKT pathway activation was more frequently seen in patients with low and high-intermediate risk tumors and was mainly caused by a combination of KRAS mutation and complete loss of PTEN expression (Figure 1). Although not significant, DFS of patients with high PI3K-AKT pathway activation seemed decreased compared to those with no or moderate activation (Figure 1). High Stathmin expression was more frequently found in high risk tumors without an association with DFS. No correlation between the degree of Stathmin expression and the degree of PI3K-AKT pathway activation was found (Table 2 and Figure 1).

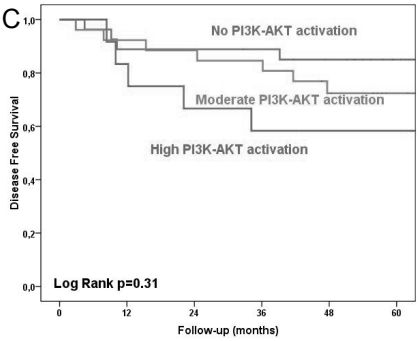
A

PI3K-AKT pathway activation			
No. Patients	*PI3K*	*KRAS*	Loss of PTEN
PI3K	5	1	1
KRAS		3	10
Loss of PTEN			18
Total	7	14	29

B

PI3K-Akt pathway	Stathmin negative		Stathmin positive		Total
	No.	%	No.	%	No.
No activation	18	66.7	9	33.3	27
Moderate activation	16	61.5	10	38.5	26
High activation	8	66.7	4	33.3	12
Total	42	64.6	23	35.4	65

C



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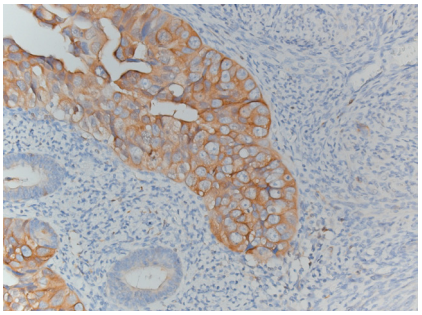


Figure 1A-D. PI3K-Akt pathway activation and the role of Stathmin. (A) Cross correlation table of components of the PI3K-AKT pathway. High PI3K-AKT pathway activation (red fields): tumors having 2 or more altered components of the pathway, moderate activation: 1 altered component and no activation: none of the components showed alterations. In 7 patients a PI3K mutation was found of whom 1 had a simultaneous mutation in KRAS and 1 patient had loss of PTEN. (B) No correlation between the degree of PI3K-AKT pathway activation and Stathmin expression on immunohistochemistry. (C) Degree of PI3K-AKT pathway activation is not significantly associated with DFS, with trend that high Pi3K-AKT pathway activation is indicative for a worse DFS. (D) Stathmin protein expression shows positive cytoplasmic staining of the tumor cells and negative normal endometrial glands for comparison.

ß-catenin / Wnt-signaling pathway

Nuclear staining of ß-catenin as a marker for an activated Wnt-signaling pathway was found in 9 tumors (14%) and infrequently found in combination with other alterations (Figure 4). Staining was only seen in low and high-intermediate risk tumors without any relation to DFS.

P53 pathway

P53 protein overexpression, assessed by immunohistochemical staining, was found in 17% of the tumors and was highly predictive for decreased DFS (Table 2 and Figure 2). Sequencing of TP53 (exons 4-8) succeeded in 48 patients and revealed 9 (14%) functional and 4 (6%) non-functional mutations (Figure 2 and Table Web Appendix 2). There was high agreement between immunohistochemical staining and sequencing of TP53 (Kappa 0.86).

Microsatellite Instability (MSI)

MSI was found in 12 tumors (19%), with a significantly higher frequency of MSI with increasing depth of myometrial invasion and increasing tumor grade (Table 2). The methylation status of the MLH-1 promoter region was successfully assessed in 9 patients and was hypermethylated in 8 patients. One patient was found to have a MSH6 germline mutation (confirming Lynch syndrome) and developed a colon carcinoma during follow-up. MSI was predictive for decreased DFS (Figure 3), and was found to be mutually exclusive with P53 overexpression (Figure 4).

Accumulation of alterations in oncogenic pathways

An alteration in one of the four main mechanisms of endometrioid type carcinogenesis (PI3K-AKT, Wnt/ß-catenin, P53 pathways and MSI) was found in 60% (39/65). In a Cox regression model that included age and deep myometrial invasion, P53 status was found to be the strongest (HR 6.7, 95%CI 1.75 – 26.0, p=0.006) single alteration to predict for a decreased disease free survival, followed by MSI (Figure 4).

In order to analyze the prognostic impact of the accumulation of alterations in the oncogenic pathways, three groups were defined: no altered pathway; one altered pathway; two or more altered pathways. When the factor accumulated altered oncogenic pathways was entered in the regression analysis (including age and deep myometrial invasion) followed by P53 overexpression and MSI, it was the only factor that remained significantly predictive for decreased DFS (HR 5.0; 95%CI 1.59 – 15.6 p=0.006, Figure 4). This finding was confirmed in the subgroup of true-HIR patients (Figure Appendix). Five out of 65 (8%) EEC patients had two or more activated pathways, and all died due to early disease recurrence (Figure 4). In contrast, 24 patients (40%) had no activated pathway of whom only one patient developed a recurrence.

Table 2. Alterations in the most common mechanisms of endometrioid type tumor carcinogenesis.

	Low Risk		High-intermediate Risk		High Risk			Total		Recurrence		Disease Free Survival
	No.	%	No.	%	No.	%	p-value*	No.	%	No.	%	Log rank p-value
Total	23	35.4	26	40.0	16	24.6		65	100	15	23.1%	
PI3K-Akt pathway alterations												
PI3K												
Wildtype	20	34.5	22	37.9	16	27.6	0.27	58	89.2	13	22.4	0.81
Mutated	3	42.9	4	57.1	0	0		7	10.8	2	28.6	
KRAS												
Wildtype	17	33.3	21	41.2	13	25.5	0.80	51	78.5	11	21.6	0.84
Mutated	6	42.9	5	35.7	3	21.4		14	21.5	4	28.6	
PTEN												
Functional PTEN	17	50.0	9	26.5	8	23.5	0.12	34	52.3	4	13.8	*0.065*
Loss of PTEN	6	20.7	15	51.7	8	27.6		29	44.6	10	34.5	
Missing	0	0	2	100	0	0		2	3.1	1	50.0	
PI3K-Akt pathway												
No Activation	13	48.1	8	29.6	6	22.2	0.14	27	41.5	4	14.8	0.31
Moderate Activation	5	19.2	12	46.2	9	34.6		26	40.0	6	23.1	
High Activation	5	41.7	6	50.0	1	8.3		12	18.5	5	41.7	
Stathmin (STMN1)												
Absent / Low	13	38.2	18	52.9	3	8.8	**<0.001**	34	52.3	8	23.5	0.82
Intermediate	4	50.0	4	50.0	0	0		8	12.3	2	25.0	
High	6	26.1	4	17.4	13	56.5		23	35.4	5	21,.7	
P53 alterations												
P53 by Immunohistochemistry												
Negative	21	39.6	18	34.0	14	26.4	0.18	53	81.5	8	15.1	**0.003**
Positive	2	18.2	7	63.6	2	18.2		11	16.9	6	54.5	
Missing	0	0	1	100	0	0		1	1.5	1	21.9	
P53 by Sequencing‡												
Wildtype	14	40.0	13	37.1	8	22.9	0.15	35	53.8	5	14.3	**<0.001**
Functional Mutation	1	11.1	7	77.8	1	11.1		9	13.8	6	66.7	
Non-functional Mutation	1	25.0	1	25.0	2	50.0		4	6.2	1	25.0	
Missing	7	41.2	5	29.4	5	29.4		17	26.2	3	17.6	
Micro Satelite Instability												
Micro Satelite Stable	22	42.3	21	40.4	9	17.3	**0.007**	52	80.0	9	17.3	**0.02**
Micro Satelite Instable	1	8.3	4	33.3	7	58.3		12	18.5	5	41.7	
Missing	0	0	1	100	0	0		1	1.5	1	100	
Wnt signaling pathway alterations												
β-Catenin: nuclear staining												
Absent	18	32.1	22	39.3	16	28.6	0.15	56	86.2	12	21.4	0.54
Present	5	55.6	4	44.4	0	0		9	13.8	3	33.3	
Accumulation of Altered Oncogenic Mechanisms												
No Altered Mechanims	10	38.5	10	38.5	6	23.1	*0.08*	26	40.0	1	3.8	**<0.001**
1 Altered Mechanism	13	38.2	11	32.4	10	29.4		34	52.3	9	26.5	
≥ 2 Altered Mechanisms	0	0	5	100	0	0		5	7.7	5	100	

*p-value by $\chi 2$ method, p-values <0.05 in bold and between 0.05 and 0.10 in italic. ‡One patient had a functional and non-functional mutaion (Web Appendix Table 2.).

Figure 2A-D.
TP53 mutations in endometrioid endometrial cancer. (A) HE stain of an EC with endometrioid grade 1 morphology; note the glandular architecture with nuclear stratification. (B) *This case showed strong nuclear P53 staining by immunohistochemistry, indicative for TP53 mutation.* (C) *TP53 mutation was confirmed by sequencing. The upper pane shows wild type sequence for reference and the lower pane shows the sample sequence. In this case a single-nucleotide substitution, cytosine (C) to thymine (T) at position 12523 in exon5 (↓) was found, resulting in a histidine (H) to tyrosine (Y) substitution at position 179 of TP53.* (D) *P53 staining by immunohistochemistry was the strongest single prognostic factor associated with a lower disease free survival on univariate analysis and multivariate analysis (HR 6.7, 95%CI 1.75 – 26.0, p=0.006).*

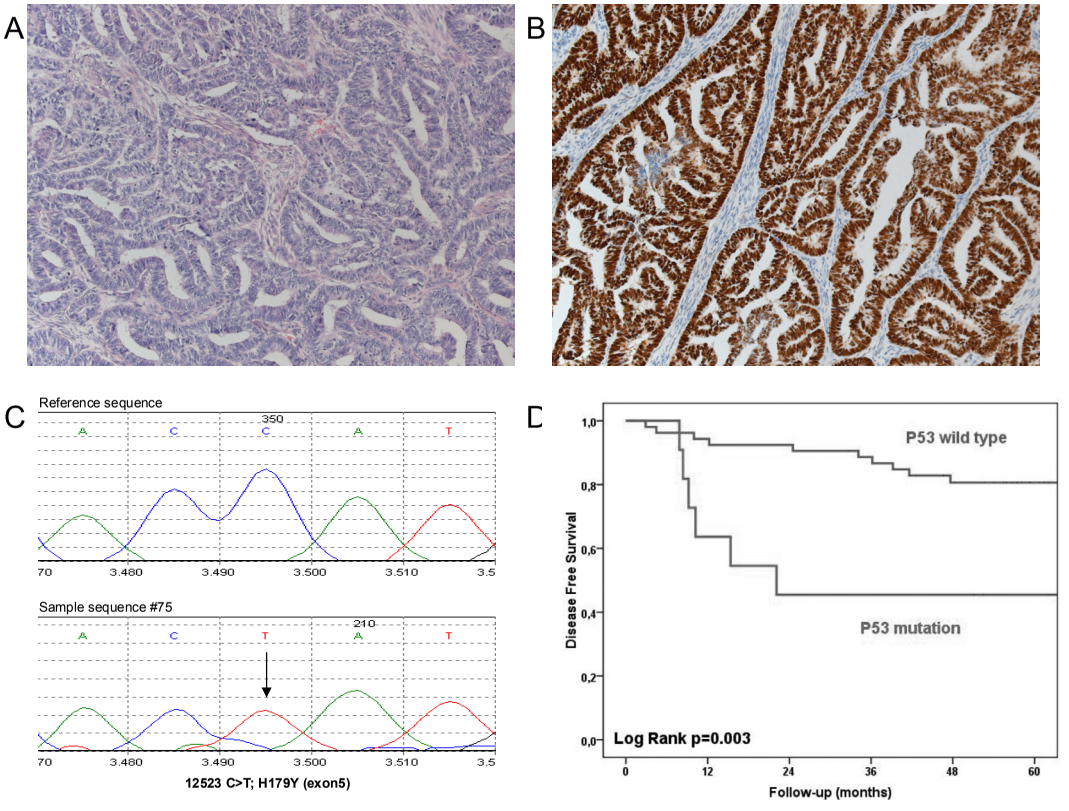
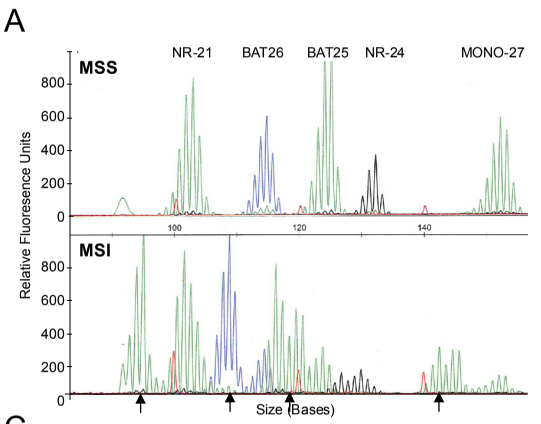
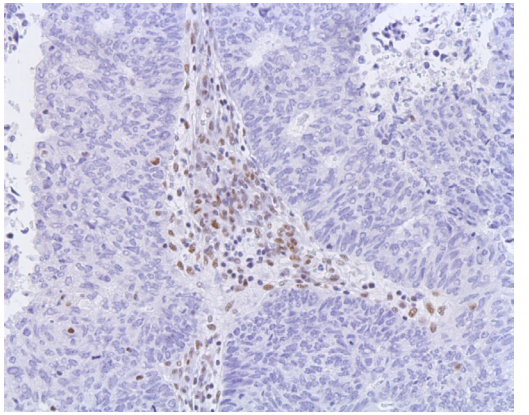
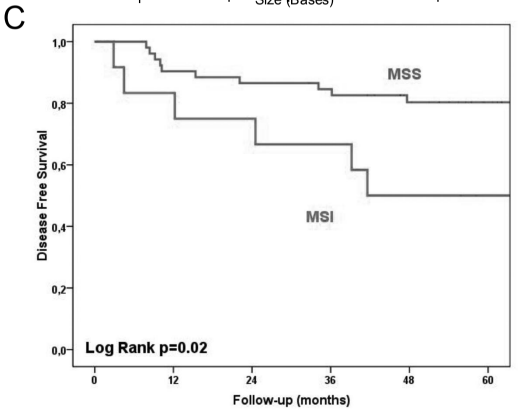


Figure 3A-C.
Microsatellite instability (MSI) and MLH-1 status. (A) Example of a MSI (lower pane) tumor sample analyzed by an ABI PRISM genetic analyzer, and the allelic pattern of the sample is shown. The presence of new alleles (↑) can be appreciated when compared to a microsatellite stable (MSS, upper pane) tumor sample. When 2 or more markers showed new alleles the sample was considered to be MSI. (B) MLH-1 immunohistochemistry confirmed MLH-1 downregulation in tumor cells; note the positive internal nuclear staining in the stroma cells. (C) Presence of MSI is prognostic for an inferior disease free survival on univariate analysis and in multivariate analysis (HR 5.3, 95%CI 1.36 – 20.9, p=0.016).







Discussion

Over the past decades prospective randomized trials have provided a solid basis for the use of clinicopathological prognostic factors such as age, grade and myometrial invasion for risk-based adjuvant therapy.[5,6] The vast majority of patients with EEC have either low (55%) or high-intermediate risk features (30%) and have a good prognosis. The present study was undertaken to investigate whether combined analysis of genetic alterations in the main involved pathways of endometrioid type carcinogenesis improved the current risk assessment on an individual basis, with the ultimate goal to further reduce both over- and undertreatment.

Although all PORTEC-2 trial patients were randomized under the condition of having HIR features at central pathology review diagnosed a subset of 14% was diagnosed with low-risk (LR) or high-risk (HR) features.[7] Incorporation of these patients into this study enabled the detection of alterations in oncogenic mechanisms in all three risk groups (LR, true-HIR, HR). In addition, patients with HIR features confirmed at central review (true-HIR) were selected for disease-related events in order to correlate the alterations in oncogenic pathways with disease recurrence. An obvious advantage of using this trial population is the relative homogeneity of the study cohort. All patients were diagnosed with EEC and were treated in a comparable manner with a long and well documented follow-up (median 7.3 years).

Although TP53 mutations have frequently (80-90%) been found in non-endometrioid endometrial cancer (NEEC), they are found in 10-15% of the EEC.[9,10] In this study 17% of the EEC tumors showed P53 overexpression. For validation purposes, TP53 (exons 4-8) was sequenced and showed a high agreement with the immunohistochemical staining (Kappa 0.86). P53 overexpression was the strongest independent prognostic pathway for decreased DFS. This finding supports the assumption that P53-positive endometrial cancers, independent of their morphology, should be considered as intrinsically aggressive tumors.

Microsatellite instability (MSI) was demonstrated in 19% of the tumors and correlated with depth of myometrial invasion and grade. Although this frequency is in line with other studies (20%-45%)[9,10], its relation with other pathological factors remains controversial. In many previous MSI studies[20-23], patient cohorts including both early and advanced FIGO stages, and cancers of different

histological subtypes, may have blurred the evaluation of the prognostic value of MSI. In our cohort, MSI was mainly caused by hypermethylation of the promoter region of MLH-1. MSI as an oncogenic mechanism was found to be mutually exclusive with P53 overexpression and clearly associated in our study with decreased DFS. A similar inverse relationship between TP53 mutations and MSI status was recently found in gastric cancer.[24] The authors hypothesized that this may be explained by alterations in an emerging tumor suppressor gene, ARID1a (component of the SWI/SNF chromatin remodeling complex), that may constitute an alternative pathway of carcinogenesis strongly associated with MSI and independent of TP53 that drives cancer development through epigenetic modifications. Recent studies have shown frequent ARID1a mutations in gynecologic cancers, including endometrial cancer.[25]

The accumulation of molecular alterations in the PI3K-AKT pathway showed a trend toward a worse clinical outcome (Figure 1). It did not reach statistical significance probably due to the small sample size. The PI3K-AKT pathway is one of the most frequent deregulated pathways in cancer and has been associated with aggressive tumor behavior in endometrial cancers.[12] The well known oncogen KRAS and tumorsuppressor PTEN converge on the PI3K-AKT pathway, resulting in growth, proliferation and survival signaling.[26,27] In addition, 'hot spot' mutations in the kinase and helical domains of PI3K confer constitutive kinase activity and thereby directly activate PI3K-AKT signaling.[28] Our data show considerable coexistence between these molecular alterations, suggesting that individual mutations are not completely redundant. These independent alterations activate the PI3K-AKT pathway differently, and cumulative molecular alterations may have a selective advantage.[29] It may be possible that loss of PTEN results in circumvention of negative feedback loops which result in an additive effect on PI3K-AKT pathway activation, as was found in knock-out mice experiments.[30] Based on these data, it is likely that the magnitude of PI3K-AKT pathway activation is influenced by the underlying molecular alteration(s), and that this impacts on oncogenicity.

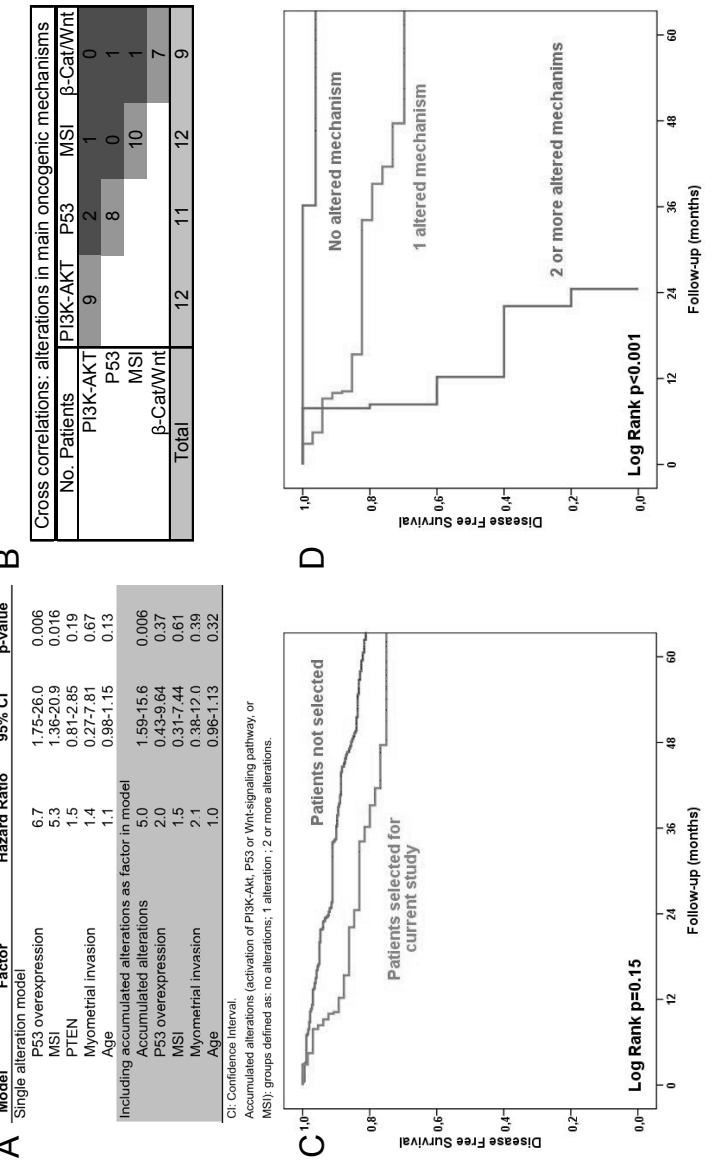


Figure 4 A-D. Accumulation of altered oncogenic mechanisms. (A) Cox regression model for effect on disease free survival of alterations in single oncogenic mechanisms. In a second model the accumulation of altered oncogenic mechanisms was entered together with oncogenic mechanisms (P53 and MSI) that were significantly associated with a decreased disease free survival on univariate analysis (Log rank p<0.1), showing that the factor accumulation of oncogenic mechanisms remained significant. (B) Table showing cross correlations between investigated oncogenic mechanisms, in red patients with 2 or more altered mechanisms and in green patients with 1 altered mechanism. PI3K-AKT pathway was activated in 12 patients of whom 2 had a P53 overexpression and 1 MSI. (C) DFS of patients selected for the current study (green, N=65) and of all unselected PORTEC-2 patients (blue, N=362). (D) DFS by accumulation of genetic alterations in PI3K-AKT, Wnt/β-catenin and P53 pathways and MSI including all patients selected for the current study (N=65).

In light of this discussion, indentifying a marker for PI3K-AKT pathway activation would be of major interest. Recently Stathmin (STMN1), a microtubule destabilizing protein, was postulated as a putative surrogate marker of the PI3K-AKT pathway with independent prognostic significance.[12,19,31] Our data do not support a clear relationship between Stathmin overexpression and PI3K-AKT pathway activation. This discrepancy may be partly explained by the difference in definition of PI3K-AKT activation. Another explanation may be that Stathmin is not only expressed in the context of activated PI3K-AKT, but also overexpressed when the TP53 tumor suppressor function is lost. This is supported by studies that show that wild-type P53 transcriptionally represses STMN1, and mutant TP53 can impair this negative regulation, leading to increased Stathmin levels.[32-34]

Mutations of multiple genes that participate in different pathways or functions may be additive or even synergistic in conferring a survival advantage to the tumor.[35] Patients with multiple activated pathways had significantly worse DFS (Figure 4). The most frequent co-occurrence was the combination of P53 and PI3K-AKT activation, which previously has been reported to be associated with a poor prognosis.[13] Taken together, these combined carcinogenic pathway alterations may better reflect the oncogenicity of tumors than their morphology, and prove to be the strongest prognostic factors.

In summary, analysis of multiple molecular genetic alterations in tissue samples of patients with EEC showed that P53 and MSI status are important independent prognostic factors for decreased DFS. The simultaneous activation of multiple oncogenic pathways was the most powerful factor predicting decreased DFS, resulting in a superior individual risk prediction as compared to the current clinicopathological approach. Although larger (prospective) series are necessary to validate these findings, our results support a biologically driven approach for individual risk assessment and treatment selection.

Reference List

1. Bray F, Loos AH, Oostindier M, Weiderpass E. Geographic and temporal variations in cancer of the corpus uteri: incidence and mortality in pre- and postmenopausal women in Europe. *Int J Cancer.* 2005;117:123-131.
2. Amant F, Moerman P, Neven P, Timmerman D, Van LE, Vergote I. Endometrial cancer. *Lancet.* 2005;366:491-505.
3. Rose PG. Endometrial carcinoma. *N Engl J Med.* 1996;335:640-649.
4. Creutzberg CL, Nout RA. The role of radiotherapy in endometrial cancer: current evidence and trends. *Curr Oncol Rep.* 2011;13:472-478.
5. Creutzberg CL, van Putten WL, Koper PC et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet.* 2000;355:1404-1411.
6. Keys HM, Roberts JA, Brunetto VL et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2004;92:744-751.
7. Nout RA, Smit VT, Putter H et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet.* 2010;375:816-823.
8. Dedes KJ, Wetterskog D, Ashworth A, Kaye SB, Reis-Filho JS. Emerging therapeutic targets in endometrial cancer. *Nat Rev Clin Oncol.* 2011;8:261-271.
9. Engelsen IB, Akslen LA, Salvesen HB. Biologic markers in endometrial cancer treatment. *APMIS.* 2009;117:693-707.
10. Samarnthai N, Hall K, Yeh IT. Molecular profiling of endometrial malignancies. *Obstet Gynecol Int.* 2010;2010:162363.
11. Oda K, Okada J, Timmerman L et al. PIK3CA cooperates with other phosphatidylinositol 3'-kinase pathway mutations to effect oncogenic transformation. *Cancer Res.* 2008;68:8127-8136.
12. Salvesen HB, Carter SL, Mannelqvist M et al. Integrated genomic profiling of endometrial carcinoma associates aggressive tumors with indicators of PI3 kinase activation. *Proc Natl Acad Sci U S A.* 2009;106:4834-4839.
13. Catasus L, Gallardo A, Cuatrecasas M, Prat J. Concomitant PI3K-AKT and p53 alterations in endometrial carcinomas are associated with poor prognosis. *Mod Pathol.* 2009;22:522-529.
14. van Eijk R, Licht J, Schrumpf M et al. Rapid KRAS, EGFR, BRAF and PIK3CA mutation analysis of fine needle aspirates from non-small-cell lung cancer using allele-specific qPCR. *PLoS One.* 2011;6:e17791.

15. Boland CR, Thibodeau SN, Hamilton SR et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res.* 1998;58:5248-5257.
16. van Roon EH, van PM, Middeldorp A et al. Early onset MSI-H colon cancer with MLH1 promoter methylation, is there a genetic predisposition? *BMC Cancer.* 2010;10:180.
17. da Costa CE, Szuhai K, van ER et al. No genomic aberrations in Langerhans cell histiocytosis as assessed by diverse molecular technologies. *Genes Chromosomes Cancer.* 2009;48:239-249.
18. Lomo L, Nucci MR, Lee KR et al. Histologic and immunohistochemical decision-making in endometrial adenocarcinoma. *Mod Pathol.* 2008;21:937-942.
19. Trovik J, Wik E, Stefansson I et al. Stathmin is superior to AKT and phospho-AKT staining for the detection of phosphoinositide 3-kinase activation and aggressive endometrial cancer. *Histopathology.* 2010;57:641-646.
20. Black D, Soslow RA, Levine DA et al. Clinicopathologic significance of defective DNA mismatch repair in endometrial carcinoma. *J Clin Oncol.* 2006;24:1745-1753.
21. Mackay HJ, Gallinger S, Tsao MS et al. Prognostic value of microsatellite instability (MSI) and PTEN expression in women with endometrial cancer: results from studies of the NCIC Clinical Trials Group (NCIC CTG). *Eur J Cancer.* 2010;46:1365-1373.
22. Percesepe A, Borghi F, Menigatti M et al. Molecular screening for hereditary nonpolyposis colorectal cancer: a prospective, population-based study. *J Clin Oncol.* 2001;19:3944-3950.
23. Zighelboim I, Goodfellow PJ, Gao F et al. Microsatellite instability and epigenetic inactivation of MLH1 and outcome of patients with endometrial carcinomas of the endometrioid type. *J Clin Oncol.* 2007;25:2042-2048.
24. Wang K, Kan J, Yuen ST et al. Exome sequencing identifies frequent mutation of ARID1A in molecular subtypes of gastric cancer. *Nat Genet.* 2011;43:1219-1223.
25. Guan B, Wang TL, Shih I. ARID1A, a factor that promotes formation of SWI/SNF-mediated chromatin remodeling, is a tumor suppressor in gynecologic cancers. *Cancer Res.* 2011;71:6718-6727.
26. Cantley LC. The phosphoinositide 3-kinase pathway. *Science.* 2002;296:1655-1657.
27. Rodriguez-Viciana P, Warne PH, Dhand R et al. Phosphatidylinositol-3-OH kinase as a direct target of Ras. *Nature.* 1994;370:527-532.
28. Samuels Y, Ericson K. Oncogenic PI3K and its role in cancer. *Curr Opin Oncol.* 2006;18:77-82.
29. Yuan TL, Cantley LC. PI3K pathway alterations in cancer: variations on a theme. *Oncogene.* 2008;27:5497-5510.
30. Kim TH, Wang J, Lee KY et al. The Synergistic Effect of Conditional Pten Loss and Oncogenic K-ras Mutation on Endometrial Cancer Development Occurs via Decreased Progesterone Receptor Action. *J Oncol.* 2010;2010:139087.

31. Saal LH, Johansson P, Holm K et al. Poor prognosis in carcinoma is associated with a gene expression signature of aberrant PTEN tumor suppressor pathway activity. *Proc Natl Acad Sci U S A.* 2007;104:7564-7569.
32. Ahn J, Murphy M, Kratowicz S, Wang A, Levine AJ, George DL. Down-regulation of the stathmin/Op18 and FKBP25 genes following p53 induction. *Oncogene.* 1999;18:5954-5958.
33. Johnsen JI, Aurelio ON, Kwaja Z et al. p53-mediated negative regulation of stathmin/Op18 expression is associated with G(2)/M cell-cycle arrest. *Int J Cancer.* 2000;88:685-691.
34. Murphy M, Ahn J, Walker KK et al. Transcriptional repression by wild-type p53 utilizes histone deacetylases, mediated by interaction with mSin3a. *Genes Dev.* 1999;13:2490-2501.
35. Yeang CH, McCormick F, Levine A. Combinatorial patterns of somatic gene mutations in cancer. FASEB J. 2008;22:2605-2622.

Appendix 1.

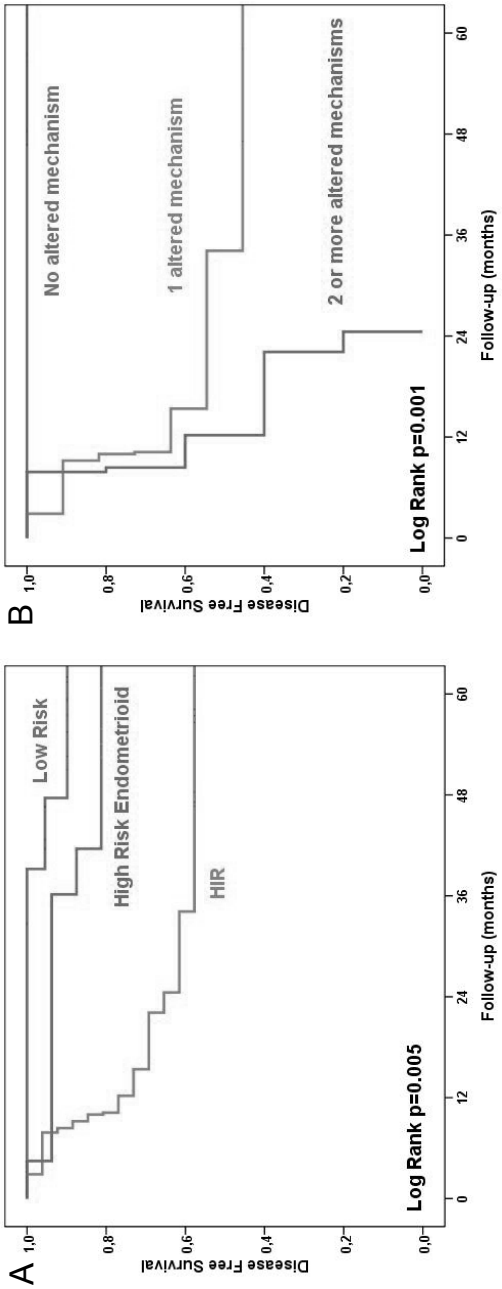


Figure 1A-B. Disease Free Survival. (A) DFS of all patients selected for the current study (N=65) by risk group based on clinicopathologic factors, see text for definitions. For this study High-intermediate risk (HIR) patients with recurrence during follow-up were selected (approximately 50%), explaining the lower than expected disease free survival of HIR patients compared to low and high risk patients in this figure. (B) DFS by accumulation of alterations in PI3K-AKT, Wnt/β-catenin and P53 pathways and MSI in patients whose HIR status was confirmed by central pathology review (N=26).

8

Discussion

The main purpose of the Post Operative Radiotherapy in Endometrial Carcinoma (PORTEC) trials has been to provide evidence with regards to risks (short and long-term treatment related morbidity) and benefits (disease control) of adjuvant radiotherapy and by doing so, further define both the indications and methods of radiotherapy with the ultimate goal to improve the overall outcome and quality of life of endometrial cancer patients. In this thesis results from the first and second PORTEC trials are presented. In the PORTEC-1 trial (1990-1997), stage I EC patients with intermediate risk features were randomized after surgery between no additional therapy and pelvic external beam radiotherapy. In the subsequent PORTEC-2 trial (2002-2006), patients with high-intermediate risk features were randomized between pelvic external beam radiotherapy and vaginal brachytherapy. In this chapter the main findings of this thesis and their implications for current patient management are discussed, focusing on future perspectives for research and treatment of endometrial cancer.

Optimal treatment for endometrial cancer patients with high-intermediate risk features

In order to decide on optimal treatment for patients with high-intermediate (HIR) features, risks (treatment related morbidity) and benefits (disease control) of different treatment strategies should be evaluated. Before reaching a conclusion, the following paragraphs discuss the key issues concerning three possible strategies after surgery: pelvic external beam radiotherapy (EBRT), vaginal brachytherapy (VBT), and no additional therapy (NAT).

Risk of disease recurrence

Evidence for the role of adjuvant radiation therapy for intermediate risk EC patients has come from four large randomised trials and a meta-analysis (Table 1).[1-5] All of these trials reached the same conclusion, that EBRT reduces the risk of locoregional (vagina and/or pelvic) recurrence approximately three-fold, but this does not lead to a decrease in the rate of distant metastasis or a benefit in overall survival. Both PORTEC-1 and GOG#99 trials have identified a subgroup of patients with HIR features that had the highest risk of locoregional recurrence without additional therapy. Based on these outcomes, the indication for adjuvant radiotherapy was only maintained for patients with HIR features. This led to a major decrease in indications for radiotherapy, sparing low-intermediate risk patients the risk of radiotherapy related morbidity.

Table 1. Randomized trials establishing the role of postoperative radiotherapy in intermediate risk endometrial cancer.

Trial (ref) acrual period	No. patients, eligibility	Surgery	Randomization	Locoregional recurrence	Survival	Severe complications
Norwegian[1] 1968–1974	540; Stage I	TAH-BSO	VBT vs VBT + EBRT	7% vs 2% at 5 years P < 0.01	89% vs 91% at 5 years P= NS	NA
PORTEC-1[3] 1990–1997	714; IB grade 2–3 IC grade 1–2	TAH-BSO	NAT vs EBRT 10-years 15-years HIR patients	14% vs 4% at 5 years P < 0.001 14% vs 5% 16% vs 6% 18% vs 5% at 5 years	85% vs 81% at 5 years P= 0.31 74% vs 68% 60% vs 52%	3% GI at 5 years, (actuarial)
GOG-99[4] 1987–1995	392; Stage IB, IC Stage II (occult)	TAH-BSO and lymphadenectomy	NAT vs EBRT HIR patients	CIR: 12% vs 3% at 2 years, P < 0.01 CIR: 26% vs 6% at 2 years	86% vs 92% at 4 years P= 0.56	8% GI at 2 years, (crude)
ASTEC/EN5[2] 1996–2005	905; Stage IAB g3, IC, Stage II, serous/cc	TAH-BSO ± lymphadenectomy	NAT vs EBRT*	7%a vs 4% at 5 years P= 0.038	84% vs 84% at 5 years P= 0.98	3 vs 7% gr 3/4
PORTEC-2 2002–2006	427, age >60 IB grade 3 IC grade 1–2 (HIR)	TAH-BSO	VBT vs EBRT	5% vs 2% at 5 years P= 0.17	85% vs 80% at 5 years P= 0.57	GI: 0.5% vs 1.9% Vagina: 1.9% vs 0.5%
Swedish[7] 1997-2008	527; Stage I medium risk	TAH-BSO	VBT vs VBT + EBRT	5% vs 1.5% at 5 years P=0.01	90% va 89% at 5 years P= 0.55	GI: 0% vs 1.8% Vagina: 0.8% vs 0%

cc: clear cell. TAH-BSO: total abdominal hysterectomy with bilateral salpingo-oophorectomy. VBT: vaginal brachytherapy.
EBRT: pelvic external beam radiotherapy. NAT: no additional therapy.
GI: gastro-intestinal. CIR: cumulative incidence of recurrence.
HIR: high intermediat risk. Medium risk: Stage I and (grade 3 or deep invasion or DNA aneuploidy) and nuclear grade 1-2
**VBT was given in both treatment arms at the discretion of the centers: EBRT 52% and NAT 51% of the patients.*

The very long-term analysis of the PORTEC-1 trial confirmed the importance of the prognostic factors age, grade and depth of myometrial invasion for selection of HIR patients. In patients with HIR features the risk of developing a locoregional recurrence was reduced from approximately 20% after NAT to 5% after EBRT. The majority (75%) of locoregional recurrences in the NAT-arm were isolated vaginal recurrences. Salvage treatment, usually consisting of EBRT combined with VBT, was most effective in patients with isolated vaginal recurrences; in 80-90% a complete remission was achieved, with 70% 5-year survival after recurrence.[6] This explains in part why upfront EBRT does not improve overall survival. In contrast, patients with isolated pelvic or combined pelvic and vaginal recurrences are at high risk of developing distant metastasis and their survival rate is similar to that of patients who initially present with distant metastasis. EBRT does not seem to prevent the development of distant metastasis, which occurred in approximately 8% of the patients in both treatment arms. Overall survival rates at 5, 10 and 15 years after treatment were approximately 80%, 65% and 50%, irrespective of receiving adjuvant radiotherapy or not. The vaginal recurrence risk of 2% at 5 years after VBT in the PORTEC-2 trial was strikingly similar to that obtained after EBRT both in PORTEC-2 and in PORTEC-1, demonstrating the efficacy of VBT in preventing vaginal recurrences. At 5 years the rate of total pelvic recurrences was 0.5% after EBRT vs. 3.8% after VBT. However, first failure analysis showed that most patients (5 of 8) with a pelvic recurrence had simultaneous distant metastases and the pelvic recurrence rate as first failure was 0.5% after EBRT vs. 1.5% after VBT, with similar rates of distant metastasis and overall survival in both arms. These findings were confirmed in a recently published Swedish trial in which 527 patients with intermediate risk EC were randomized between VBT and combined EBRT and VBT. The rate of vaginal recurrences was low in both arms of the trial (crude rates 2.7% vs. 1.9%), while in the VBT alone arm a higher rate of locoregional recurrences was found (5.0% vs 1.5% at 5 years, p=0.01) without differences in 5-year relapse-free (86 vs 87%) and overall survival (89 vs 90%), results very similar to those of PORTEC-2.[7] For approximately 3% of patients EBRT might be beneficial compared to VBT in preventing both vaginal and pelvic lymph node recurrences, but as distant

metastasis will ultimately dictate their prognosis and overall survival is not improved, this benefit is debatable.Due to the low total number of vaginal and pelvic events in PORTEC-2, a multivariate analysis of prognostic factors for pelvic recurrence was not included in the publication of the outcome analysis. The GOG99 trial investigators identified lymph vascular space invasion (LVSI) as an independent prognostic factor for any relapse and included LVSI in their HIR definition.[4] Other authors have confirmed the strong adverse prognostic impact of LVSI, both in presence and absence of nodal metastases[8,9] In the PORTEC-1 analysis which included the registered group with grade 3 EC with deep invasion, LVSI was also found to be a risk factor, especially for distant relapse.[10] The Swedish trial included DNA-aneuploidy in their definition and did not include LVSI or age.[7] Despite the differences in HIR definitions, testing of the GOG HIR definition in the PORTEC-1 analysis yielded very similar results. In clinical practice, LVSI should be considered an adverse factor and as such, grade 3 EC with superficial invasion but with clear LVSI is considered high-risk, and these patients receive EBRT and are eligible for trials investigating chemotherapy, such as PORTEC-3 and GOG249. Similarly, grade 2 with very deep invasion close to the serosa and clear LVSI represents the upper end of the HIR spectrum and might also be considered high risk.

Overall survival and recurrence rates for patients with HIR features in PORTEC-2 were remarkably similar to those obtained in all of the randomized trials in patients with intermediate risk EC (Table 1). From a clinical point of view, given that low-intermediate risk patients do not receive adjuvant treatment and are in fact regarded low risk, patients with HIR features have become the intermediate group. Thus, it would seem more appropriate to group current low-risk and low-intermediate risk features as low risk EC, and designate those with HIR features as intermediate risk EC, which would be in line with the prognosis and therapeutic consequences.

Radiotherapy related morbidities and their impact on health-related quality of life

In the randomised trials (Table 1) increased early and late (physician-reported) adverse event rates were reported after EBRT, as compared to NAT.[1-4] In PORTEC-1 late toxicity was reported in 6% of patients in the NAT arm and

in 25% after EBRT. Approximately two-thirds of adverse events (AE) in the EBRT arm were mild (grade 1), while 3% were grade 3 complications, with the vast majority of AE related to the gastro-intestinal (GI) tract. In PORTEC-2 the increased gastro-intestinal acute toxicity in the EBRT arm decreased from 6 months onwards, and the difference between the EBRT and VBT arms lost its significance after 24 months. Both HRQL analyses in the PORTEC-1 and PORTEC-2 trials have provided unique insight into the impact these symptoms have on patient-reported health related quality of life (HRQL), and how long this impact persists in the years following treatment.

With HRQL studies the question always remains what size of difference between scores reflects a clinical meaningful or relevant difference. Studies on the magnitude of clinically relevant differences agree on a minimum difference of 5% to 10% of the instrument range as being clinically relevant.[14-16] For the EORTC Core questionnaire, Osoba et al. found that patients valued a change of 5-10% as 'little', 10-20% as 'moderate' and more than 20% as 'very much' difference.[15] These descriptions are used to value the observed differences in HRQL scores.

In the PORTEC-2 trial, EBRT was associated with an early increase of patient reported bowel symptoms (very much diarrhea and little fecal leakage), while scores after VBT remained at baseline level in range of those of an age-matched Dutch norm-population. In the years following treatment the bowel symptoms gradually decreased but remained moderately to a little higher than those of VBT patients and the norm-population. Even in patients treated 12 to 19 years ago with EBRT in PORTEC-1, bowel symptoms were still moderately increased compared to NAT patients. Interestingly, after the longer follow-up period in PORTEC-1, urinary urgency and incontinence were moderately increased after EBRT. While the bladder is known to be a late responding organ, the combination of increased rates of fecal leakage and urinary incontinence are suggestive for a decrease in pelvic floor function.[17-20] In terms of clinical relevance perhaps the most straightforward finding in the long-term PORTEC-1 analysis was the increased use of incontinence materials day and night after EBRT (43% vs 15%), thus very much difference.

Importantly there were clear relationships between increased bowel and bladder symptoms and the moderately increased need to remain close to the toilet, and between increased limitation in daily activities due to these

symptoms and decreased social and (role-) physical functioning. This pattern of combined bowel symptoms and decreased social and (role-) physical functioning was also observed in the Swedish trial that compared VBT alone with the combination of EBRT and VBT.[21] In the PORTEC-1 HRQL questionnaire there was space at the end of the questionnaire for additional comments, several patients commented in there own words on this relationship: 'frequent and unpredictable bowel movements make me uncertain, so I don't leave the house', 'radiotherapy gave me irritated bowels, so I have to keep in mind if there is a toilet in my direct vicinity' and 'when I leave the house for a day trip I always take a loperamide for my stool'. Finally, both from 6 months after treatment onwards in PORTEC-2 and in PORTEC-1 the general functioning scores of both treatment groups did not differ from those of an age-matched Dutch norm population, indicating that for most women the diagnosis and treatment for endometrial cancer has a clear but transient influence on their general functioning.

Both in PORTEC-1 and PORTEC-2 there was no difference in patient reported sexual functioning and symptoms between both treatment arms. In both trials quite a few patients indicated on the questionnaire forms that they were widowed, did not have a partner, or that their partner had a medical condition that withheld them from being sexually active, resulting in a lower response rate to these questions. In PORTEC-2 sexual activity increased from 15% at baseline after surgery to 39% at 6 months, reaching a plateau at a slightly lower level in both treatment arms compared to the age-matched norm population. The increase in sexual activity in the 6 months following treatment was most apparent in patients younger than 65 years, while very few patients older than 75 years were sexually active which did not change over time. In PORTEC-1 there was no difference in sexual activity between both treatment arms, suggesting that the slight decrease in sexual activity in PORTEC-2 patients compared to the age-matched norm population is not radiotherapy related. A statement on one of the returned questionnaires provides meaningful insight: 'for me it was important my spouse had consideration for my situation; sexual changes need adjustment and creativity'.

Advances in pelvic external beam radiotherapy

As with all studies looking at the late effects of treatment, important progress has been made in the delivery of EBRT since 1990 when the first patients were treated in the PORTEC-1 trial. Intensity modulated and image-guided radiotherapy (IMRT, IGRT), have led to a more conformal dose distribution with increased sparing of normal (bowel and bladder) tissues (Figure 1).[22-24]

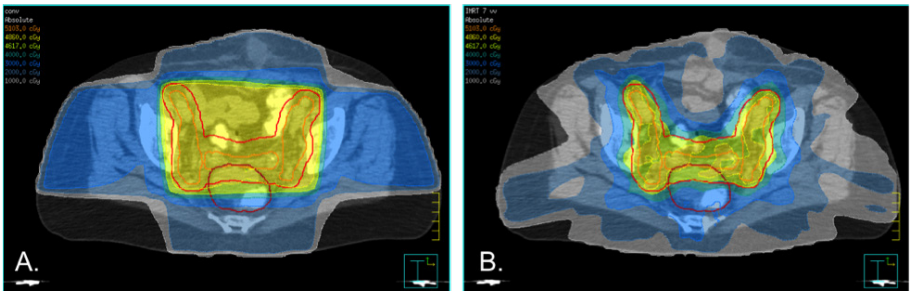


Figure 1. Dose distribution of pelvic external beam radiotherapy; in yellow 95% isodose of 46 Gy. (A) 3-dimensional conformal radiotherapy dose distribution (B) Intensity modulated radiotherapy (IMRT).

Approximately 52% of the patients in PORTEC-1 were treated with a four-field box technique and 18% with a 3-field technique with some form of individualized shielding, while 30% were treated with parallel opposing fields. The use of multiple fields significantly reduced the rate of late complications compared to parallel opposing fields, which increased exposure of bowel structures to high dose levels.[25] Nonetheless, a four-field box technique with individual shielding was required in PORTEC-2 and still led to increased gastro-intestinal toxicity and related sequelae at least up to 5-years after treatment. Studies using IMRT for gynaecological cancer have shown that this leads to more bowel and bladder sparing and less early and late bowel toxicity compared to historic controls. Early results of the RTOG-0418 in which 58 EC patients were included from 25 institutions found a non-significant reduction of short-term bowel adverse event rate of 28% after IMRT compared to 40% in historic controls.[26] Mundt et al. have reported a reduction in early (40 patients, GI grade 2: 60% vs 91% for IMRT vs conventional historic controls) and late (36 patients, median follow-up 19 months, GI all grades: 11% vs 50%) GI toxicity in patients treated for cervical cancer.[27,28] Due to interfraction motion of the target volume due to differences in bladder and rectal filling, even with IMRT

considerable margins are needed to ensure adequate target coverage during the whole period of external beam treatment.[29,30] Further improvement is expected from strategies that incorporate interfraction motion of the target volumes and organs at risk (i.e. IGRT), resulting in reduced margins.[24] Results of studies using IGRT, including daily online soft tissue position verification protocols and a 'treatment plan of the day' concept are being awaited. In the mean time IMRT is an important step forward in reducing treatment related toxicity in patients that need EBRT.

Vaginal brachytherapy: current issues

VBT has been used as adjuvant treatment for EC patients for several decades. A wide variety of dose and fractionation schedules and treated length of the vagina have been reported, resulting in low rates of vaginal recurrences and treatment related toxicity (Table 2).[31-42] However, most studies were retrospective and most included a significant proportion of low to low-intermediate risk patients, which makes it difficult to draw definite conclusions with regard to efficacy.

With increasing dose and increasing irradiated vaginal length, the risk of associated toxicity such as atrophy and shortening of the vagina increases.[36] In a randomized trial reported by Sorbe et al, 290 low-risk EC patients were allocated to receive either 15 Gy in 2.5 Gy fractions, or 30 Gy in 5 Gy fractions of HDR brachytherapy specified at the surface over a period of 8 days.[40] The mean vaginal shortening measured by colpometry was 0.3 cm in the 15 Gy group (ns), and 2.1 cm in the 30 Gy group ($p < 0.001$) at 5 years. In addition, mucosal atrophy and bleeding were significantly more frequent in the 30 Gy group, demonstrating a clear dose-effect relationship.

In PORTEC-2 a dose and fractionation schedule was chosen with the aim to give a similar biological effective dose to the proximal vagina as with EBRT. The dose was specified at 5 mm depth from the surface and top of the cylinder in order to include the full vaginal wall. Due to the steep dose gradient with brachytherapy, the dose from the specification isodose at 5 mm depth towards the surface of the cylinder increases considerably, which can explain the increase rate of grade 2 in mucosal atrophy observed during gynaecological examination after VBT compared to EBRT.[43]

Table 2. Results of postoperative vaginal brachytherapy for endometrial cancer.

Author (ref) acrual period	No. patients, eligibility	Treatment	Vaginal recurrence	Locoregional recurrence	Survival	Severe complications
Institutional series including at least 100 patients						
Sorbe et al.[35] publ 1990	404; Stage I		0,7%	3,0%	92% OS at 5-years	6.9% significant
MacLeod et al.[31] 1985-1993	141; Stage I-IIIA	4 x 8.5 Gy at surface	1,4%	2,0%	91% OS at 5-years	no grade 3/4
Weiss et al.[36] 1987-1993	122; Stage I-II	3 x 7 Gy at surface	1,6%	4,1%	94% NED at 5-years	no grade 3/4
Eltabbakh et al.[28] 1958-1994	332; Stage IA grd 1-2	1 x 30 Gy LDR at surface	0,0%	0,6%	99% DFS at 5-years	2.1% grade 3/4
Petereit et al.[32] 1989-1997	191; Stage IA grd 1-2	2 x 16.2 Gy at surface ovoids	0,0%	0,5%	95% OS at 5-years	0.5% grade 4
Anderson et al.[26] 1990-1996	102; Stage I	3 x 5 Gy at 0.5 cm	1,0%	1,9%	84% OS at 5-years	no grade 3/4
Horowitz et al.[29] 1989-1999	164; Stage I-II	3 x 7Gy at 0.5 cm	1,2%	0,6%	87% OS at 5-years	no grade 3/4
Alektiar et al.[25] 1987-2002	382; Stage I-II	3 x 7Gy at 0.5 cm	0,8%	0,0%	93% OS at 5-years	0.5% grd 3/0.3% grd 4
Solhjem et al.[33] 1998-2004	100; Stage I grd 2-3 and IB grd 1-2 if >2cm	3 x 7Gy at 0.5 cm	0,0%	0,0%	98% OS at 3-years	no grade 3/4
Ataham et al.[27] 1994-2005	128; Stage I	5 x 5.5 Gy at 0.5 cm	0,0%	1,6%	96% OS at 5-years	no grade 3/4

Studies with different brachytherapy dose levels						
Kloetzer et al.[30]	108; Stage I-II	4 x 10 Gy at 0.5 cm	0,0%	2,2%	98% OS at 3-years	2.2% / 0.0% grade 3/4
1981-1990		4 x 10 Gy at 1 cm	3,1%	3,1%	97% OS at 3-years	6.2% / 3.1% grade 3/4
		4 x 10 Gy at 1 cm + vagina	0,0%	0,0%	97% OS at 3-years	6.8% / 12.6% grade 3/4
Osrund et al.[37]	217; Stage I-II	4 x 5.5 Gy at 0.5 cm	1,0%			26% / 8% grade 1/2
1988-1996		4 x 5.5 Gy individualized at 0.3-0.4-0.5 cm	2,5%			17% / 1% grade 1/2 no grade 3/4
Sorbe et al.[34]	290; Stage IA grd 1-2	6 x 2.5 Gy at 0.5 cm vs.	0,7%	1,4%	95% OS at 5-years	vaginal shortening
1989-2003		6 x 5.0 Gy at 0.5 cm				0.3 cm vs. 2.1 cm
Randomized trial VBT versus NAT in low risk endometrial cancer						
Sorbe et al.[47]	645; Stage 1A grade 1-2	3 to 6 x 3 to 8 Gy	1,2%	2,6%	96% OS at 5-years	no grade 3/4
1995-2004		at 0.5 cm vs. NAT	3,1%			
Randomized trials VBT versus EBRT +/- VBT in (high) intermediate risk endometrial cancer						
Norwegian[1]	540; Stage I	1 x 60 Gy LDR at surface		6,9%	91% OS at 5-years	1% grade 4
1968–1974		vs. EBRT + same VBT		1,9%	89% OS at 5-years	1.1% grade 4/5
PORTEC-2	427, age >60 IA grade 3	3 x 7Gy at 0.5 cm vs.	1,8%	5,1%	85% OS at 5-years	GI: VBT 0.5% vs 1.9%
2002–2006	IB grade 1–2 (HIR)	EBRT	1,6%	2,1%	80% OS at 5-years	Vagina: 1.9% vs 0.5%
Swedish[7]	527; Stage I and	6 x 3 Gy at 0.5 cm	2.7%*	5,0%	90% OS at 5-years	grd 3 VBT vs EBRT + VBT
1997-2008	(grade 3 or deep invasion	3 x 5.9 Gy at 0.5 cm				GI: 0% vs 2%
	or DNA aneuploidy) and	1 x 20 Gy LDR at 0.5 cm				Vagina: 0.8% vs 0%
	nuclear grade 1-2	vs. EBRT + same VBT	1.9%*	1,5%	89% OS at 5-years	

LDR: low dose rate. VBT: vaginal brachytherapy. NAT: no adjuvant therapy. NED: no evidence of disease. OS: overall survival
*crude rate or vaginal recurrence

More recently a study examining vaginal wall specimens found that most lymph vessels are located in the superficial 3 mm of the vaginal wall.[44] While 3-dimensional delineation and treatment planning are mainstay in virtually all tumor sites in radiation oncology, VBT planning has largely remained 2-dimensional. Few studies have used CT for analysis of dose to organs at risk, but CT fails in visualizing the target volume since the vaginal wall cannot be clearly distinguished from the bladder and rectal wall on CT.[45-48] In a pilot study of 10 patients for whom MRI scans were obtained with the vaginal cylinder in treatment position, the maximal distance from the surface of the cylinder to the outer border of the vaginal wall did not exceed 3 mm in dorso-ventral direction, while in the lateral directions the distance was 5 mm on average (Figure 2).[49] However, in the upper (proximal) third of the vagina on the lateral sides, folds of the vaginal wall were observed where the distance from the applicator surface to the outer border of the vaginal wall exceeded 5 mm.

Although excellent vaginal control was seen using a standardized treatment prescription in PORTEC-2, underdosage in these lateral vaginal folds can provide a possible explanation for the very few vaginal recurrences seen after brachytherapy. These results suggest that the brachytherapy prescription dose in the doso-ventral direction could be reduced compared to the lateral sides, and support a more individualized image guided approach. Although such asymmetrical dose distributions can be obtained using multichannel cylinders, care must be taken with regard to an increased mucosal surface dose.[50] Future studies examining the most optimal dose and fractionation schedule as well as target definition and type of applicator ensuring optimal target coverage are warranted.

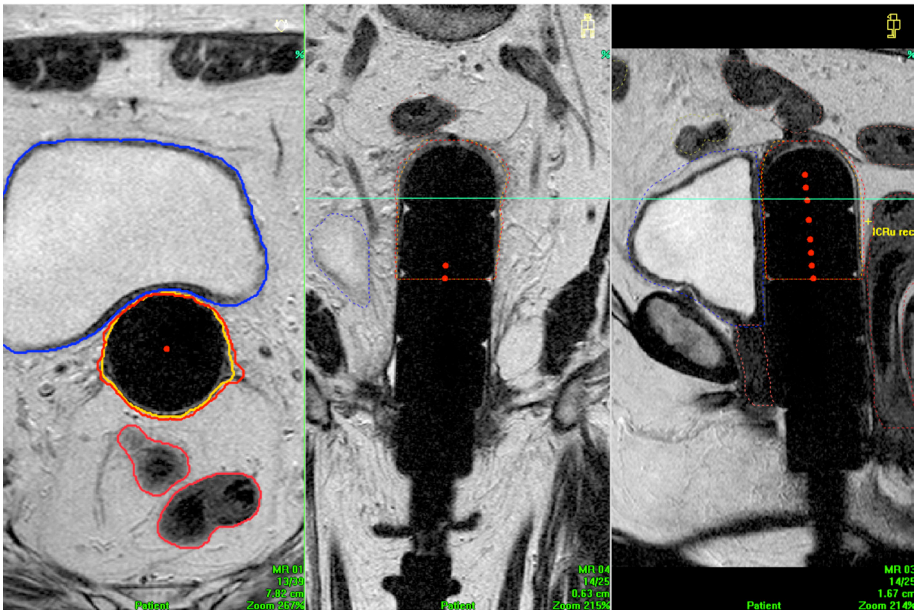


Figure 2. Axial, coronal and sagittal MRI scan of vaginal brachytherapy cylinder in treatment position. A clinical target volume was contoured by two observers (red, orange), organs at risk by one (bladder in blue, rectum in brown).

Optimal treatment for patients with high-intermediate risk features

Taken together, both PORTEC-1 and PORTEC-2 have provided evidence with regard to risks and benefits of three adjuvant treatment strategies for HIR patients: EBRT, VBT or NAT. EBRT leads to an important reduction in the risk of locoregional recurrence, without leading to a reduction in the rate distant metastasis or a benefit in overall survival compared to NAT. Both EBRT and VBT offer similar rates of vaginal control, distant metastasis and overall survival. However, as discussed above, for approximately 3% of patients EBRT might be beneficial in preventing both vaginal and pelvic lymph node recurrences compared to VBT. Since the majority of patients with a pelvic lymph node recurrence have simultaneous distant metastases, overall survival is not improved, and this potential benefit of EBRT is debatable.

Despite the fact that EC patients in general are elderly with frequent co-morbid conditions such as obesity, diabetes and hypertension, patients with HIR features have a good prognosis and given the increasing population of long-term survivors, both short and long-term treatment related symptoms and their impact on quality of life should be taken into account when deciding

on optimal treatment for these patients. EBRT is associated with long-lasting bowel and bladder symptoms that impact on patient functioning up to 15 years after treatment. VBT is clearly more favourable, with equal vaginal control and HRQL results similar to an age-matched norm population.

When opting for no additional treatment, only the 15-20% patients that develop a recurrence are exposed to salvage treatment. Salvage treatment usually consists of combined EBRT and VBT and offers a high probability of local control but with a risk of increased toxicity compared with EBRT alone.[51-53] However, HRQL and symptom outcome of 14 patients who received salvage treatment for a recurrence in the NAT arm of PORTEC-1 was very similar to that of patients initially treated with EBRT alone. VBT (18-24 Gy in 3-6 fractions) has only been compared to observation in a single, small randomized trial that only included low risk patients.[54] There was no significant difference in the vaginal recurrence rate (VBT 1.2% vs observation 3.1%, p=0.11) and there were few and mild (grade 1-2) side effects. Potential risks of this strategy that remain unquantified are the psychological impact of a watchful waiting policy, and the burden, stress and anxieties of experiencing a recurrence and subsequent more intensive treatment.[55] Finally, there is a lack of data on patient preferences with regard to risks versus benefits of NAT vs VBT.

With the aim to provide both an answer to the question if VBT is more favorable than NAT in terms of reduction of overtreatment, health impact and costs, and ultimate vaginal control, and if a lower dose of VBT is equally effective compared to the standard dose, the PORTEC-4 has been initiated.[56] The recently started PORTEC-4 trial is a multicenter randomized trial in which patients with HIR features are randomly allocated (2:1) to vaginal brachytherapy and observation after surgery, and in the VBT arm 1:1 to the standard dose of 21 Gy in 3 fractions of 7 Gy and the lower dose level (3 fractions of 5 Gy). The primary endpoint is vaginal recurrence and the second primary endpoint is the 5-year probability of vaginal control, including treatment for vaginal relapse. The objective of the brachytherapy dose comparison is to estimate the differences in vaginal relapse, toxicity and quality of life (with emphasis on sexual symptoms and functioning) with sufficient precision. Imaging with CT or MRI with the vaginal cylinder inserted will be performed to provide more detailed data on target volume and doses to rectum and bladder. Importantly,

both patient and health care provider preferences with regard to risks versus benefits of VBT or observation are being investigated in a medical decision making side study to PORTEC-4.

At present, vaginal brachytherapy offers a highly effective therapy to prevent vaginal recurrences and maximize relapse-free survival with a favorable toxicity and HRQL profile and is therefore currently the treatment of choice.

Current issues and future perspectives in adjuvant treatment of endometrial cancer

Improving the outcome of high risk patients

The prognosis of the 15% of EC patients with high risk features, being those with grade 3 and deep invasion, with more advanced stages, or serous or clearcell histology, is predominantly determined by the higher risk of distant metastases.[10,57,58] Improvement of the prognosis of these patients depends on systemic therapy that is effective in preventing the development of distant metastases. Therefore, ongoing trials focus on establishing the role of chemotherapy, either given alone or in combination with radiotherapy. In the ongoing PORTEC-3 trial EBRT alone is compared with combined chemotherapy and EBRT (two cycles of cisplatin during radiotherapy followed by four adjuvant cycles of carboplatin and paclitaxel) in high risk patients.[59] In this trial upfront pathology review is mandatory to ensure only high risk patients are included. Quality of life is assessed which will play an important role in the weighing of risks versus benefits of more intensified treatment in these elderly patients. In the GOG#249 trial stage I-II patients with high-intermediate or high risk features are randomized between EBRT alone and VBT followed by adjuvant chemotherapy (3 cycles of carboplatin and paclitaxel).[60] This trial will potentially answer two questions: if VBT followed by adjuvant chemotherapy can further decrease the relatively low risk of pelvic and distant recurrences in high-intermediate risk patients (and at which cost); and how the toxicity profile of EBRT compares to the combination of VBT and short-course adjuvant chemotherapy. The GOG#258 trial compares the same combined radiotherapy and chemotherapy schedule used in the PORTEC-3 trial with chemotherapy

alone (6 cycles of carboplatin and paclitaxel alone) in patients with stage III and IVA endometrial cancer.[61] This trial will answer the question if there is a role for EBRT at all in patients with advanced stage disease, who are mainly at risk of distant relapse. It is expected that the implementation of technical advances in EBRT such as IMRT and IGRT (discussed in the previous section) will decrease external beam radiotherapy related morbidity. Outcomes of ongoing phase II and III randomized trials comparing IMRT with 3D conformal EBRT including quality of life analysis are awaited.[62,63]

While ongoing trials all use the combination of carboplatin and paclitaxcel chemotherapy, knowledge of the biology of endometrial cancer and the underlying pathways that play a role in the development and disease progression is accumulating. Drugs targeting specific pathways known to be of importance in EC have mainly been tested as single agents in phase I and II trials.[64] Since targeted therapies are in clinical use in several types of cancer, more evidence has emerged that a major mechanism of targeted therapy resistance lies in the propensity of tumors to use alternative pathways.[65] Similar to the use of different classical chemotherapeutic agents during a course of chemotherapy, it is expected that multiple targeted agents will need to be used that block several alternative pathways simultaneously.[66] An alternative approach that is being investigated is to target pathways further downstream where alternating routes converge.

Can we further decrease over- and undertreatment in endometrial cancer in the future?

Implementation of the high-intermediate risk criteria to select patients for radiotherapy has led to a substantial reduction of indications for radiotherapy. Nonetheless, there still remains considerable overtreatment and to a lesser extent undertreatment: approximately 5% of the low or low-intermediate risk patients develop recurrent or metastatic disease; approximately 7 patients with HIR features need to be receive VBT to prevent 1 vaginal recurrence and this does not prevent the development of distant metastasis in approximately 8% of the patients; and finally a substantial proportion of high risk patients do not develop metastases and might not have needed adjuvant treatment. An

attractive way to further refine the currently used system for risk assessment is to incorporate new molecular prognostic factors that may better predict the biology, risk of recurrence and metastatic propensity of individual tumours.
Several studies have investigated the prognostic capacity of genetic alterations involved in endometrial carcinogenesis.[64,67-69] For endometrioid type tumors, the majority of studies indicate that activation of the Wnt/ß-catenin signaling pathway is associated with a good prognosis, while mutation of *TP53* and activation of the PI3K-AKT pathway are indicators of tumors with a more aggressive clinical course. Conflicting results have been reported with regard to the prognostic significance of MSI and mutations in PTEN and KRAS as components of the PI3K-AKT pathway. However, most studies are relative small, retrospective and include a heterogenous group of patients including both higher FIGO stages and a combination of endometrioid type and non-endometrioid type tumors and focus on one or two pathways. For these reasons genetic alterations are not yet used as prognostic factors to tailor treatment.
In the pilot study undertaken in 65 selected PORTEC-2 patients, the aim was to investigate these four important pathways simultaneous in a relative homogenous cohort of patients with a similar prognosis based on clincopathologic factors. The combination of multiple activated pathways was the most powerful prognostic factor for decreased disease free survival in a multivariate analysis that included depth of myometrial invasion and age. The most frequent co-occurrence was the combination of *TP53* mutation and PI3K-AKT activation, which has previously been reported to be associated with a poor prognosis.[70] Multiple pathway activation, found in 8% of patients, was strongly associated with aggressive clinical course. In contrast, 40% of patients had no alterations in the investigated pathways and had a very low risk of disease progression. These results indicate that molecular prognostic factors can potentially refine the currently used system for risk classification and lead to a further decrease of over- and undertreatment. Confirmation and further refinement of these findings in a large sample of patients including un-irradiated controls is pivotal. For this purpose a future study is planned using tumor samples of patients from both the PORTEC-1 and PORTEC-2 trials. In future, analysis of tumor samples of patients treated in the PORTEC-3 trial will

provide insight alterations that are predictive for response to chemotherapy, both in endometrioid and non-endometrioid types, and provide rationale for patient selection and future trials incorporating targeted therapies.

Despite their older age at diagnosis and frequent comorbid conditions, the overall prognosis of endometrial cancer patients is good. Improved selection of patients at risk of recurrent and metastastic disease will decrease over- and undertreatment and will be pivotal for future studies applying targeted therapies. In the process of shared decision making on optimal adjuvant therapy, patients need to be informed not only on benefits concerning risk reduction, but also on risks of treatment related morbidity. Quality of life analysis plays a critical role in the interpretation of physician-reported adverse events, and knowledge of the impact treatment related symptoms have on the everyday life of patients. In the near future, the use of postoperative radiotherapy and brachytherapy will be increasingly tailored to the individual patient's needs, sparing many low and intermediate risk patients unnecessary toxicities while identifying the few who need adjuvant treatment, and improving outcomes for patients with high risk disease.

References

1. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. *Obstet.Gynecol.* 1980;56(4):419-427.
2. Blake P, Swart AM, Orton J, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. *Lancet.* 2009;373(9658):137-146.
3. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet.* 2000;355(9213):1404-1411.
4. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol.Oncol.* 2004;92(3):744-751.
5. Kong A, Johnson N, Kitchener HC, Lawrie TA. Adjuvant radiotherapy for stage I endometrial cancer. *Cochrane Database Syst Rev.* 2012;3:CD003916.
6. Creutzberg CL, van Putten WL, Koper PC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. *Gynecol.Oncol.* 2003;89(2):201-209.
7. Sorbe B, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B. External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma--a prospective randomized study. *International journal of radiation oncology, biology, physics.* Mar 1 2012;82(3):1249-1255.
8. Briet JM, Hollema H, Reesink N, et al. Lymphvascular space involvement: an independent prognostic factor in endometrial cancer. *Gynecologic oncology.* Mar 2005;96(3):799-804.
9. Cohn DE, Horowitz NS, Mutch DG, Kim SM, Manolitsas T, Fowler JM. Should the presence of lymphvascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? *Gynecologic oncology.* Dec 2002;87(3):243-246.
10. Creutzberg CL, van Putten WL, Warlam-Rodenhuis CC, et al. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial. *J.Clin.Oncol.* 2004;22(7):1234-1241.
11. Scholten AN, van Putten WL, Beerman H, et al. Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. *Int.J.Radiat.Oncol.Biol.Phys.* 2005;63(3):834-838.

12. Lax SF, Kurman RJ, Pizer ES, Wu L, Ronnett BM. A binary architectural grading system for uterine endometrial endometrioid carcinoma has superior reproducibility compared with FIGO grading and identifies subsets of advance-stage tumors with favorable and unfavorable prognosis. *The American journal of surgical pathology.* Sep 2000;24(9):1201-1208.
13. Scholten AN, Smit VT, Beerman H, van Putten WL, Creutzberg CL. Prognostic significance and interobserver variability of histologic grading systems for endometrial carcinoma. *Cancer.* 2004;100(4):764-772.
14. Barrett B, Brown D, Mundt M, Brown R. Sufficiently important difference: expanding the framework of clinical significance. *Med.Decis.Making.* 2005;25(3):250-261.
15. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J.Clin.Oncol.* 1998;16(1):139-144.
16. Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. *Cancer.* 2007;110(1):196-202.
17. Viswanathan AN, Yorke ED, Marks LB, Eifel PJ, Shipley WU. Radiation dose-volume effects of the urinary bladder. *International journal of radiation oncology, biology, physics.* Mar 1 2010;76(3 Suppl):S116-122.
18. Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *International journal of radiation oncology, biology, physics.* Mar 30 1995;31(5):1257-1280.
19. Hazewinkel MH, Sprangers MA, van dV, et al. Long-term cervical cancer survivors suffer from pelvic floor symptoms: a cross-sectional matched cohort study. *Gynecol. Oncol.* 2010;117(2):281-286.
20. Lind H, Waldenstrom AC, Dunberger G, et al. Late symptoms in long-term gynaecological cancer survivors after radiation therapy: a population-based cohort study. *British journal of cancer.* Sep 6 2011;105(6):737-745.
21. Sorbe BG, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B. External Pelvic and Vaginal Irradiation Versus Vaginal Irradiation Alone as Postoperative Therapy in Medium-Risk Endometrial Carcinoma: A Prospective, Randomized Study-Quality-of-Life Analysis. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society.* Sep 2012;22(7):1281-1288.
22. Beriwal S, Jain SK, Heron DE, et al. Clinical outcome with adjuvant treatment of endometrial carcinoma using intensity-modulated radiation therapy. *Gynecologic oncology.* Aug 2006;102(2):195-199.
23. Heron DE, Gerszten K, Selvaraj RN, et al. Conventional 3D conformal versus intensity-modulated radiotherapy for the adjuvant treatment of gynecologic malignancies: a comparative dosimetric study of dose-volume histograms small star, filled. *Gynecologic oncology.* Oct 2003;91(1):39-45.
24. Monroe AT, Pikaart D, Peddada AV. Clinical outcomes of image guided radiation therapy (IGRT) with gold fiducial vaginal cuff markers for high-risk endometrial cancer. *Acta Oncol.* Sep 24 2012.

25. Creutzberg CL, van Putten WL, Koper PC, et al. The morbidity of treatment for patients with Stage I endometrial cancer: results from a randomized trial. *Int.J.Radiat.Oncol.Biol.Phys.* 2001;51(5):1246-1255.
26. Jhingran A, Winter K, Portelance L, et al. A Phase II Study of Intensity Modulated Radiation Therapy to the Pelvis for Postoperative Patients With Endometrial Carcinoma: Radiation Therapy Oncology Group Trial 0418. *International journal of radiation oncology, biology, physics.* Sep 1 2012;84(1):e23-28.
27. Mundt AJ, Lujan AE, Rotmensch J, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *International journal of radiation oncology, biology, physics.* Apr 1 2002;52(5):1330-1337.
28. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *International journal of radiation oncology, biology, physics.* Aug 1 2003;56(5):1354-1360.
29. Jurgenliemk-Schulz IM, Toet-Bosma MZ, de Kort GA, et al. Internal motion of the vagina after hysterectomy for gynaecological cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* Feb 2011;98(2):244-248.
30. Harris EE, Latifi K, Rusthoven C, Javedan K, Forster K. Assessment of organ motion in postoperative endometrial and cervical cancer patients treated with intensity-modulated radiation therapy. *International journal of radiation oncology, biology, physics.* Nov 15 2011;81(4):e645-650.
31. Alektiar KM, Venkatraman E, Chi DS, Barakat RR. Intravaginal brachytherapy alone for intermediate-risk endometrial cancer. *Int.J.Radiat.Oncol.Biol.Phys.* 2005;62(1):111-117.
32. Anderson JM, Stea B, Hallum AV, Rogoff E, Childers J. High-dose-rate postoperative vaginal cuff irradiation alone for stage IB and IC endometrial cancer. *International journal of radiation oncology, biology, physics.* Jan 15 2000;46(2):417-425.
33. Atahan IL, Ozyar E, Yildiz F, et al. Vaginal high dose rate brachytherapy alone in patients with intermediate- to high-risk stage I endometrial carcinoma after radical surgery. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society.* Nov-Dec 2008;18(6):1294-1299.
34. Eltabbakh GH, Piver MS, Hempling RE, Shin KH. Excellent long-term survival and absence of vaginal recurrences in 332 patients with low-risk stage I endometrial adenocarcinoma treated with hysterectomy and vaginal brachytherapy without formal staging lymph node sampling: report of a prospective trial. *Int.J.Radiat.Oncol.Biol.Phys.* 1997;38(2):373-380.
35. Horowitz NS, Peters WA, III, Smith MR, Drescher CW, Atwood M, Mate TP. Adjuvant high dose rate vaginal brachytherapy as treatment of stage I and II endometrial carcinoma. *Obstet.Gynecol.* 2002;99(2):235-240.

36. Kloetzer KH, Gunther R, Wendt T. [The vaginal stump recurrence rate in endometrial carcinoma in relation to the target volume of postoperative HDR-afterloading brachytherapy]. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft ... [et al].* Jan 1997;173(1):13-17.
37. MacLeod C, Fowler A, Duval P, et al. High-dose-rate brachytherapy alone post-hysterectomy for endometrial cancer. *International journal of radiation oncology, biology, physics.* Dec 1 1998;42(5):1033-1039.
38. Petereit DG, Tannehill SP, Grosen EA, Hartenbach EM, Schink JC. Outpatient vaginal cuff brachytherapy for endometrial cancer. *Int.J.Gynecol.Cancer.* 1999;9(6):456-462.
39. Solhjem MC, Petersen IA, Haddock MG. Vaginal brachytherapy alone is sufficient adjuvant treatment of surgical stage I endometrial cancer. *Int.J.Radiat.Oncol.Biol.Phys.* 2005;62(5):1379-1384.
40. Sorbe B, Straumits A, Karlsson L. Intravaginal high-dose-rate brachytherapy for stage I endometrial cancer: a randomized study of two dose-per-fraction levels. *Int.J.Radiat.Oncol.Biol.Phys.* 2005;62(5):1385-1389.
41. Sorbe BG, Smeds AC. Postoperative vaginal irradiation with high dose rate afterloading technique in endometrial carcinoma stage I. *International journal of radiation oncology, biology, physics.* Feb 1990;18(2):305-314.
42. Weiss E, Hirnle P, Arnold-Bofinger H, Hess CF, Bamberg M. Adjuvant vaginal high-dose-rate afterloading alone in endometrial carcinoma: patterns of relapse and side effects following low-dose therapy. *Gynecologic oncology.* Oct 1998;71(1):72-76.
43. Onsrud M, Strickert T, Marthinsen AB. Late reactions after postoperative high-dose-rate intravaginal brachytherapy for endometrial cancer: a comparison of standardized and individualized target volumes. *International journal of radiation oncology, biology, physics.* Mar 1 2001;49(3):749-755.
44. Choo JJ, Scudiere J, Bitterman P, Dickler A, Gown AM, Zusag TW. Vaginal lymphatic channel location and its implication for intracavitary brachytherapy radiation treatment. *Brachytherapy.* 2005;4(3):236-240.
45. Holloway CL, Macklin EA, Cormack RA, Viswanathan AN. Should the organs at risk be contoured in vaginal cuff brachytherapy? *Brachytherapy.* Jul-Aug 2011;10(4):313-317.
46. Hoskin PJ, Bownes P, Summers A. The influence of applicator angle on dosimetry in vaginal vault brachytherapy. *The British journal of radiology.* Mar 2002;75(891):234-237.
47. Hung J, Shen S, De Los Santos JF, Kim RY. Image-based 3D treatment planning for vaginal cylinder brachytherapy: dosimetric effects of bladder filling on organs at risk. *International journal of radiation oncology, biology, physics.* Jul 1 2012;83(3):980-985.

48. Stewart AJ, Cormack RA, Lee H, et al. Prospective clinical trial of bladder filling and three-dimensional dosimetry in high-dose-rate vaginal cuff brachytherapy. *International journal of radiation oncology, biology, physics.* Nov 1 2008;72(3):843-848.
49. Nout RA, Jurgenliemk-Schulz IM, Laman MS, et al. Vaginal brachytherapy with MRI guidance: target volume definition and effect of bladder filling on dose to organs at risk. . *ESTRO 31 Anniversary Congress – GEC-ESTRO* Vol 99. London: Radiotherapy and Oncology; 2011:S118.
50. Tanderup K, Lindegaard JC. Multi-channel intracavitary vaginal brachytherapy using three-dimensional optimization of source geometry. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* Jan 2004;70(1):81-85.
51. Huh WK, Straughn JM, Jr., Mariani A, et al. Salvage of isolated vaginal recurrences in women with surgical stage I endometrial cancer: a multiinstitutional experience. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society.* Jul-Aug 2007;17(4):886-889.
52. Jhingran A, Burke TW, Eifel PJ. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. *Int J Radiat Oncol Biol Phys.* Aug 1 2003;56(5):1366-1372.
53. Lin LL, Grigsby PW, Powell MA, Mutch DG. Definitive radiotherapy in the management of isolated vaginal recurrences of endometrial cancer. *International journal of radiation oncology, biology, physics.* Oct 1 2005;63(2):500-504.
54. Sorbe B, Nordstrom B, Maenpaa J, et al. Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: a controlled randomized study. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society.* Jul 2009;19(5):873-878.
55. Nout RA, Creutzberg CL. Point: Vaginal brachytherapy should be a standard adjuvant treatment for intermediate-risk endometrial cancer. *Brachytherapy.* Jan-Feb 2011;10(1):1-3.
56. PORTEC-4: Postoperative Radiation Therapy for Endometrial Carcinoma Multicenter Randomised Phase III Trial Comparing Vaginal Brachytherapy (Two Dose Schedules) with Observation after Surgery. www.msbi.nl/portec4. Accessed 05-10-2012.
57. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer.* 1987;60(8 Suppl):2035-2041.
58. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics.* Nov 2006;95 Suppl 1:S105-143.

59. PORTEC-III: Randomized Phase III Trial Comparing Concurrent Chemoradiation and Adjuvant Chemotherapy With Pelvic Radiation Alone in High Risk and Advanced Stage Endometrial Carcinoma. http://clinicaltrials.gov/ct2/show/NCT00411138?term=PORTEC&rank=1. Accessed 05-10-2012.
60. GOG#249: A Phase III Trial of Pelvic Radiation Therapy Versus Vaginal Cuff Brachytherapy Followed By Paclitaxel/Carboplatin Chemotherapy in Patients With High Risk, Early Stage Endometrial Carcinoma. http://clinicaltrials.gov/ct2/results?term=NCT00807768&Search=Search. Accessed 05-10-2012.
61. GOG#258: A Randomized Phase III Trial of Cisplatin and Tumor Volume Directed Irradiation Followed by Carboplatin and Paclitaxel vs. Carboplatin and Paclitaxel for Optimally Debulked, Advanced Endometrial Carcinoma. http://clinicaltrials.gov/ct2/results?term=NCT00942357&Search=Search. Accessed 05-10-2012.
62. Prospective Randomised Phase II Trial Evaluating Adjuvant Pelvic Radiotherapy Using Either IMRT or 3-Dimensional Planning for Endometrial Cancer. http://clinicaltrials.gov/ct2/results?term=NCT01164150&Search=Search. Accessed 05-10-2012.
63. Phase III Study Comparing 3D Conformal Radiotherapy and Conformal Radiotherapy IMRT to Treat Endometrial Cancer of 70 Years Old Women : Contribution of Oncogeriatric Evaluation to the Study of Acute Toxicity. http://clinicaltrials.gov/ct2/results?term=NCT01641497&Search=Search. Accessed 05-10-2012.
64. Dedes KJ, Wetterskog D, Ashworth A, Kaye SB, Reis-Filho JS. Emerging therapeutic targets in endometrial cancer. *Nat.Rev.Clin.Oncol.* 2011;8(5):261-271.
65. Sebolt-Leopold JS, English JM. Mechanisms of drug inhibition of signalling molecules. *Nature.* May 25 2006;441(7092):457-462.
66. Kummar S, Chen HX, Wright J, et al. Utilizing targeted cancer therapeutic agents in combination: novel approaches and urgent requirements. *Nature reviews. Drug discovery.* Nov 2010;9(11):843-856.
67. Engelsen IB, Akslen LA, Salvesen HB. Biologic markers in endometrial cancer treatment. *APMIS.* 2009;117(10):693-707.
68. Samarnthai N, Hall K, Yeh IT. Molecular profiling of endometrial malignancies. *Obstet.Gynecol.Int.* 2010;2010:162363.
69. Silverberg S.G. MGL, Kurman R.J. Tumors of the Uterine Corpus. *Pathology and Genetics of Tumours of the Breast and Female Genital Organs*. Lyon: IARCPress; 2003:217-257.
70. Catasus L, Gallardo A, Cuatrecasas M, Prat J. Concomitant PI3K-AKT and p53 alterations in endometrial carcinomas are associated with poor prognosis. *Mod. Pathol.* 2009;22(4):522-529.

Summary

Introduction

Chapter 1 provides a general introduction into the background and treatment of endometrial cancer (EC). This thesis presents results of two randomized trials investigating the role of Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC). The PORTEC-1 trial (1990-1997) randomly allocated 714 EC patients with intermediate risk features to postoperative external beam radiotherapy (EBRT) or no additional treatment (NAT). After completion of PORTEC-1, the indication for RT was restricted to patients with 2 of the so-called high-intermediate risk (HIR) factors (age >60, grade 3 or deep invasion). In the subsequent PORTEC-2 trial (2002-2006) the role of vaginal brachytherapy (VBT) was investigated. In PORTEC-2, 427 EC patients with HIR features were randomly allocated to EBRT or vaginal brachytherapy (VBT).

The aims of this thesis were:
1) To establish the role of VBT in terms of efficacy, treatment related morbidity and patient-reported health related quality of life (HRQL) as compared to EBRT for patients with HIR features.
2) To analyze the long-term outcomes of the PORTEC-1 trial, especially with regard to HRQL of the long-term cancer survivors.
3) To investigate whether adverse molecular prognostic factors can improve the current risk assessment based on clinicopathological factors.

The role of postoperative vaginal brachytherapy in high-intermediate risk endometrial cancer; results of the PORTEC-2 trial.

The final efficacy analysis of the PORTEC-2 trial is reported in chapter 3. With a median follow-up of 45 months there were very few vaginal recurrences in both treatment arms: estimated 5-year vaginal recurrence rates were 1.6% after EBRT vs. 1.8% after VBT (p=0.74). There was no significant difference in the 5-year locoregional (vaginal and/or pelvic) recurrence rate (2.1% vs. 5.1%, p=0.17), despite a higher total pelvic recurrence rate after VBT (0.5% vs. 3.8%, p=0.02). First failure analysis showed that most patients (5 of 8) with a pelvic recurrence had simultaneous distant metastases and the 5-year rate of pelvic

recurrence as first failure were 0.5% after EBRT vs. 1.5% after VBT (p=0.30). There were no differences in the five-year rates of distant metastasis (5.7% vs. 8.3%) and overall survival (79.8% vs. 78.6%).
An initial increase of physician-reported grade 1 and 2 gastro-intestinal (GI) morbidity was observed directly after EBRT (53% vs. 12% for VBT) that decreased during further follow-up, while for VBT there was no increase compared to baseline. Morbidity of the vaginal mucosa was assessed during gynaecological examination and showed an increase of grade 1 to 2 mucosal atrophy in both treatment arms, with more grade 2 atrophy from 6 months onwards after VBT, as compared to EBRT. There were few serious (grade 3) adverse events (GI bowel obstruction requiring surgery in 4 EBRT patients vs. 1 VBT patient; marked vaginal atrophy with or without shortening or narrowing in 1 vs. 4 patients).

Patient-reported HRQL during the first two years after treatment is described in **chapter 2** and the subsequent analysis up to five years, including a comparison with an age-matched Dutch norm population, is described in **chapter 6**. With a high response rate of 81%, marked differences in HRQL between both treatment groups were found. Bowel symptoms such as diarrhea and fecal leakage were significantly increased after EBRT as compared to VBT. After EBRT, 15.4% and 7.3% of the patients reported “quite a bit” or “very much” diarrhea, whereas after VBT these rates were 2.8% and 2.8%. Fecal leakage was reported by 3.4% (quite a bit) and 1.7% (very much) patients who had EBRT, vs. 0.7% and 0% for VBT, respectively. Although these bowel symptoms showed a decline during further follow-up, they remained increased in patients treated with EBRT, both compared to patients who had VBT and to the age-matched norm population. Among VBT patients, bowel symptoms did not increase over baseline and remained similar to those of the norm population. Importantly, for patients treated with EBRT the increased bowel symptoms led to a higher need to remain close to a toilet, more limitations of daily activities and a lower social functioning, which persisted up to five years after treatment. Global health and functioning scales were lowest at baseline after surgery, and recovered during the first 6 months to reach a plateau within range of the norm population.

These results indicate that for most women the stressful period of diagnosis and treatment for endometrial cancer has a clear but transient influence on their general functioning.
In this population of elderly women reported sexually activity rates increased during the first 6 months after treatment, without differences in sexual functioning or symptoms between the treatment groups. However, sexual activity rates of both groups were a little lower than those of the age-matched norm population.

Fifteen-year results of the PORTEC-1 trial and health related quality of life of the long-term cancer survivors.
In **chapter 4** the HRQL analysis of life of the long-term cancer survivors from the PORTEC-1 trial is reported. The questionnaire response rate was 70%, with a median follow-up of 13 years. Patients treated with EBRT reported significantly increased bowel and bladder symptoms, most notably urinary urgency and incontinence, diarrhea with frequency and urgency and fecal leakage, as compared to those who had surgery alone (NAT). The increased symptom rates are reflected by the frequent use of incontinence materials after EBRT: 43% of patients reported day and night use of incontinence pads, in contrast to 15% of patients who were observed after surgery. Patients treated with EBRT reported more limitations of daily activities due to bowel and urinary symptoms and lower physical and role-physical functioning. There were no differences between both treatment groups with regard to sexual functioning or symptoms. As expected, there were more patients in the NAT group who had survived a locoregional recurrence and had undergone salvage therapy. These patients reported higher levels of fecal urgency and fecal leakage, with a trend towards more urinary urgency and urinary incontinence, similar to the patients in the EBRT group.
The very long-term outcomes with regard to the primary and secondary endpoints of the PORTEC-1 trial are reported in **chapter 5**. At the time of analysis 426 patients were alive with a median follow-up of 13 years. Fifteen-year locoregional recurrence rates were 6% for EBRT vs. 16% for NAT ($p<0.0001$), while 15-year rates distant metastasis (9% vs 7%, $p=0.25$) and overall survival

(52% vs 60%, p=0.14) were similar. Most (74%) of the locoregional recurrences in the NAT group were vaginal recurrences. Multivariate analysis confirmed the prognostic significance of grade 3, age >60 years and deep myometrial invasion for locoregional recurrence and endometrial cancer related death, confirming the relevance of HIR criteria for treatment selection. For patients with HIR features the locoregional recurrence rate without radiotherapy was approximately 20% at 5 and 10 years, compared to 5% after EBRT. Again, there were no differences in rates of distant metastases and overall survival for patients with HIR features. Estimated 10-year survival after vaginal recurrence was 51% vs. 25% for NAT vs EBRT; 18% vs 0% after pelvic relapse and 8% vs 4% after distant relapse. These results indicate that salvage therapy for vaginal recurrences is effective, while pelvic recurrences have a more dismal outcome, similar to patients with distant metastasis.

The role of molecular prognostic factors in the refinement of the current risk based strategy for adjuvant therapy in endometrial cancer.

The results of a pilot study investigating the prognostic significance of alterations in the main pathways involved in endometrioid type carcinogenesis (PI3K-AKT pathway, Wnt/β-catenin-signaling, microsatellite-instability and mutational activation of TP53) are described in chapter 7. Formalin-fixed paraffin embedded tissue samples of 65 selected patients who participated in the PORTEC-2 trial were analysed. P53 status and MSI were the strongest single genetic prognostic factors for decreased disease free survival, while high PI3K-AKT pathway activation showed a trend and β-catenin was not prognostic. However, the combination of multiple activated pathways was the most powerful prognostic factor for decreased disease free survival in multivariate analysis. Activation of multiple pathways, found in 8% of patients, was strongly associated with an aggressive clinical course. In contrast, 40% of patients had no alterations in the investigated pathways and had a very low risk of disease progression. These results indicate that molecular prognostic factors can be used to refine the currently used system for risk classification and may lead to a further decrease of over- and undertreatment.

Discussion

Chapter 8 discusses the main findings presented in this thesis and their implications, including a future outlook for the treatment and research for EC. The 15-year results of the PORTEC-1 trial confirm the importance of the prognostic factors age, grade and depth of myometrial invasion for selection of HIR patients (approximately 30% of EC patients). EBRT leads to an important reduction in the risk of locoregional recurrence (mainly due to a decrease in vaginal recurrences), without a survival benefit compared to NAT. The PORTEC-2 trial has shown that EBRT and VBT offer excellent rates of vaginal control and similar overall survival for patients with HIR features, while VBT has a clearly more favourable treatment related morbidity and HRQL profile, with results similar to an age-matched norm population. It has become clear that EBRT is associated with long-lasting bowel symptoms that impact on patients' daily lives and physical functioning, even 10-15 years after treatment. Therefore, VBT is currently the treatment of choice for patients with HIR features.

It can be argued that VBT is still overtreatment, since approximately 7 HIR patients need VBT to prevent 1 recurrence and postoperative radiotherapy does not lead to a survival benefit. When opting for no additional treatment after surgery, only the 20% patients that develop a recurrence are exposed to salvage treatment, usually a combination of EBRT and VBT, that has more treatment related morbidity and impact on HRQL than VBT alone. In order to provide both an answer to the question if NAT is more favorable than VBT in terms of reduction of overtreatment, health impact and costs, with similar ultimate vaginal control, and to the question if a lower VBT dose is equally effective compared to the standard dose, the PORTEC-4 has been initiated. In PORTEC-4, EC patients with HIR features are randomly allocated (2:1) to vaginal brachytherapy and observation after surgery, and in the VBT arm 1:1 to the standard dose of 21 Gy in 3 fractions of 7 Gy and the lower dose level (3 fractions of 5 Gy).

EBRT has remained only indicated in the 15% EC patients with high risk features. Ongoing trials (PORTEC-3, GOG#249 and GOG#258) focus on establishing the role of chemotherapy either alone or in combination with radiotherapy in these patients.

Another attractive way to further decrease over- and undertreatment in EC is to incorporate new molecular prognostic factors in the currently used system for risk classification based on clinicopathological factores. The pilot study in 65 selected PORTEC-2 patients showed that P53 status and MSI were the strongest single genetic prognostic factors. However, the combination of multiple activated pathways was the most powerful prognostic factor for decreased disease free survival in multivariate analysis, indicating that molecular prognostic factors can potentially refine the currently used system for risk classification. Confirmation of these findings in a large sample of patients including unirradiated controls is pivotal. For this purpose a future study is planned using tumor tissue samples of patients from both PORTEC-1 and PORTEC-2 trials. In addition, future analysis of tumor samples of patients treated in the PORTEC-3 trial will provide insight in molecular alterations that are predictive for response to chemotherapy, both in endometrioid and non-endometrioid types, and provide rationale for future trials incorporating targeted agents.

In the near future both the use and technique of postoperative radiotherapy and image-guided VBT will be increasingly tailored to the individual patient's needs, sparing low risk patients unnecessary treatment related toxicity and improving outcomes for high risk EC patients.

Nederlandse samenvatting

Introductie

In **Hoofdstuk 1** wordt een algemene inleiding gegeven over de achtergrond en behandeling van endometriumcarcinoom (baarmoederkanker). In dit proefschrift worden de resultaten van twee gerandomiseerde trials naar de rol van Post-Operatieve RadioTherapie in de behandeling van EndometriumCarcinoom (PORTEC) beschreven. In de PORTEC-1 trial (1990-1997) werden 714 endometriumcarcinoom patiënten met intermediaire risicofactoren gerandomiseerd tussen postoperatieve uitwendige radiotherapie en geen aanvullende behandeling na de operatie. Uitwendige radiotherapie gaf een significante verlaging van het risico op het optreden van een locoregionaal recidief (in de vagina en/of lymfklieren in het bekken); dit leidde echter niet tot een verbetering in de 5-jaars overleving. Er werden drie belangrijke risicofactoren gevonden voor het optreden van een locoregionaal recidief: leeftijd 60 jaar of ouder, graad 3 en diepe myometriuminvasie. Voor patiënten met twee van deze drie risicofactoren was de verlaging in het risico op een locoregionaal recidief het grootst. Na afloop van deze trial werd de indicatie voor radiotherapie dan ook beperkt tot patiënten met twee van de drie risicofactoren: de zogenaamde 'hoog-intermediaire' risicogroep. Omdat de meeste (75%) recidieven in het diepst gelegen deel van de vagina optraden werd in de daaropvolgende PORTEC-2 trial (2002-2006) de waarde van vaginale brachytherapie (inwendige bestraling) onderzocht. In PORTEC-2 werden 427 endometriumcarcinoom patiënten met hoog-intermediare risicofactoren gerandomiseerd tussen uitwendige radiotherapie of vaginale brachytherapie.

De doelstellingen van dit proefschrift zijn:

1) Onderzoeken van de waarde van vaginale brachytherapie in vergelijking met uitwendige radiotherapie voor patiënten met endometriumcarcinoom met hoog-intermediaire risicofactoren in de PORTEC-2 studie, zowel wat betreft de effectiviteit, behandelingsgerelateerde morbiditeit als door de patiënt gerapporteerde kwaliteit van leven.

2) De lange termijn uitkomsten van de PORTEC-1 studie te analyseren, met name wat betreft de kwaliteit van leven van de lange termijn overlevenden.

3) Te onderzoeken of moleculaire prognostische factoren de huidige op klinisch-pathologische factoren gebaseerde risico-inschatting (en indicatiestelling voor adjuvante behandeling) kunnen verbeteren.

De rol van postoperatieve vaginale brachytherapie in hoog-intermediair risico endometriumcarcinoom patiënten: resultaten van de PORTEC-2 trial. **Hoofdstuk 3** beschrijft de uitkomsten van de analyse van de effectiviteit van de behandeling in de PORTEC-2 trial. Met een mediane follow-up duur van 45 maanden waren er zeer weinig vaginale recidieven in beide behandelingsarmen: het geschatte 5-jaars vaginaal recidief risico bedroeg 1.6% na uitwendige radiotherapie en 1.8% na vaginale brachytherapie (p=0.74). Ondanks het hogere totaal risico op een lymfklier recidief in het bekken na vaginale brachytherapie (0.5% vs. 3.8%, p=0.02), leidde dit niet tot een significant verschil in het 5-jaars locoregionaal recidief risico. Analyse van het eerste recidief toonde aan dat de meeste patiënten (5 van de 8) met een lymfklier recidief in het bekken ook afstandsmetastasen hadden, en dat het 5-jaars risico op een lymfklier recidief in het bekken als enige (solitaire) recidief 0.5% na uitwendige radiotherapie en 1.5% na vaginale brachytherapie (p=0.30) bedroeg. Er was geen verschil tussen de behandelingsgroepen in de kans op afstandsmetastasen na 5 jaar (5.7% vs. 8.3%) of de 5-jaars kans op overleving (79.8% vs. 78.6%).
Direct na afloop van de uitwendige radiotherapie werd een toename van de door de artsen gerapporteerde graad 1 en 2 gastro-intestinale morbiditeit gevonden (53% na uitwendige radiotherapie vs. 12% na vaginale brachytherapie), die vervolgens afnam tijdens de verdere follow-up, terwijl er na vaginale brachytherapie geen toename gevonden werd in vergelijking met het uitgangsniveau voor start van de behandeling. Veranderingen in het vaginaslijmvlies door de radiotherapie werd geobjectiveerd tijdens het gynaecologisch onderzoek, en liet een toename zien van graad 1 en 2 atrofie in beide behandelingsarmen, met meer graad 2 atrofie vanaf 6 maanden na vaginale brachytherapie in vergelijking met uitwendige radiotherapie. Er waren weinig ernstige (graad 3) bijwerkingen (darmobstructie waarvoor operatief

ingrijpen in 4 uitwendig bestraalde patiënten vs. 1 patiënt na vaginale brachytherapie; uitgesproken vaginale atrofie met of zonder verkorting of vernauwing in 1 vs. 4 patiënten).

De resultaten van de door de patiënten zelf gerapporteerde kwaliteit van leven tijdens de eerste twee jaar na de behandeling zijn beschreven in hoofdstuk 2, en de vervolg analyse tot 5 jaar na de behandeling inclusief een vergelijking met een voor leeftijd gecorrigeerde Nederlandse normpopulatie is beschreven in **hoofdstuk 6**. Met een hoge (81%) respons op de kwaliteit van leven vragenlijsten werden markante verschillen gevonden in de kwaliteit van leven tussen beide behandelgroepen. Darm symptomen zoals diarree en verlies van beetjes ontlasting waren significant toegenomen na uitwendige radiotherapie in vergelijking met vaginale brachytherapie. Na afloop van uitwendige radiotherapie rapporteerden 15.4% en 7.3% van de patiënten “nogal” en “heel erg” diarree, terwijl dit na vaginale brachytherapie 2.8% en 2.8% bedroeg. Verlies van beetjes ontlasting werd na uitwendige radiotherapie door 3.4% van de patiënten als “nogal“ en door 1.7% als “heel erg” gerapporteerd, vergeleken met 0.7% en 0% na vaginale brachytherapie. Alhoewel de darmsymptomen afnamen tijdens de verdere follow-up, bleef een hoger percentage van de uitwendige bestraalde patiënten hier last van houden vergeleken met vaginale brachytherapie en de normpopulatie. Na vaginale brachytherapie werd geen toename in darmsymptomen gerapporteerd in vergelijking met de uitgangssituatie voor de start van de behandeling, en de darmsymptomen bleven op het niveau van de normpopulatie. Van belang hierbij is dat bij uitwendig bestraalde patiënten de darmsymptomen leidden tot een sterkere noodzaak om in de buurt van een toilet te blijven, tot meer beperkingen van dagelijkse activiteiten en tot lager sociaal functioneren, hetgeen aanhield tot 5 jaar na de behandeling. Algemene kwaliteit van leven en functioneren waren op het laagste niveau bij de uitgangsmeting na de operatie (voor de start van de bestraling), en herstelden in de eerste 6 maanden na de behandeling tot het niveau van de normpopulatie. Deze resultaten tonen aan dat voor de meeste vrouwen de stressvolle periode van diagnose en behandeling voor endometriumcarcinoom een duidelijke maar voorbijgaande invloed heeft op het algemeen functioneren.

Door deze populatie van oudere vrouwen werd een toename van seksuele activiteit (ten opzichte van kort na de operatie) gerapporteerd tijdens de eerste 6 maanden na de behandeling, zonder verschillen in seksueel functioneren of symptomen tussen de behandelgroepen. Desondanks was de seksuele activiteit in beide groepen lager dan die van de voor leeftijd gecontroleerde normpopulatie.

Vijftien-jaars resultaten van de PORTEC-1 trial en kwaliteit van leven van de lange termijn overlevenden.

In hoofdstuk 4 wordt de kwaliteit van leven analyse van de lange termijn overlevenden van de PORTEC-1 trial beschreven. De respons op de kwaliteit van leven vragenlijst was 70% met een mediane follow-up duur van 13 jaar. Na uitwendige radiotherapie rapporteerden significant meer patiënten darm- en blaassymptomen vergeleken met patiënten die geen aanvullende behandeling kregen. Deze darm- en blaassymptomen bestonden uit een toegenomen aandrang voor urine, verlies van beetjes ontlasting of urine, en diarree. Deze toename in symptomen bleek ook duidelijk uit het toegenomen gebruik van incontinentiemateriaal: na uitwendige radiotherapie droeg 43% van de patiënten dag en nacht incontinentiemateriaal, vergeleken met 15% van de patiënten die alleen de operatie hadden ondergaan. Patiënten die waren behandelend met uitwendige radiotherapie rapporteerden meer beperkingen in de dagelijkse activiteiten door darm- en blaas symptomen, en scores voor lichamelijk functioneren waren lager. Er was geen verschil tussen de behandelingsgroepen met betrekking tot seksueel functioneren en symptomen.

Zoals verwacht waren er in de groep patiënten die geen aanvullende behandeling hadden ondergaan, meer patiënten die een locoregionaal recidief hadden overleefd en daar een meer uitgebreide behandeling voor hadden ondergaan. Deze patiënten rapporteerden vaker aandrang en verlies van beetjes ontlasting, met een trend voor frequentere aandrang en ongewild verlies van urine, met scores die vergelijkbaar waren met die van de patiënten die uitwendig bestraald waren.

De zeer lange termijn uitkomsten met betrekking tot de primaire en secundaire eindpunten van de PORTEC-1 trial zijn beschreven in **hoofdstuk 5**. Ten tijde van de analyse waren 426 patiënten in leven, met een mediane follow-up van 13 jaar. Het 15-jaars locoregionale recidief risico was 6% na uitwendige radiotherapie versus 16% na geen aanvullende behandeling na de operatie ($p<0.0001$), terwijl zowel het 15-jaars risico op afstandsmetastasen (9% vs 7%, $p=0.25$) en de 15-jaars overleving (52% vs 60%, $p=0.14$) gelijk waren. De meeste (74%) locoregionale recidieven in de groep patiënten die geen aanvullende behandeling na de operatie hadden ondergaan waren gelokaliseerd in het diepst gelegen deel van de vagina, en de meeste werden alsnog succesvol behandeld. Multivariate analyse bevestigde het prognostische belang van leeftijd ouder dan 60 jaar, graad 3 en diepe myometriuminvasie voor het risico op locoregionaal recidief en endometriumcarcinoom gerelateerd overlijden, waarmee het belang van de hoog-intermediaire risico criteria voor patiëntselectie bevestigd werd. Voor patiënten met hoog-intermediare risicofactoren die geen radiotherapie hadden ondergaan was het locoregionaal recidief risico 20% na 5 en 10 jaar, vergeleken met 5% na uitwendige radiotherapie. Ook voor de patiënten met hoog-intermediare risicofactoren was er geen verschil tussen de behandelingsgroepen in risico op afstandsmetastasen en kans op overleving. De 10-jaars overleving na een vaginaal recidief was 51% in de groep die geen aanvullende behandeling na de operatie had ondergaan (en dus alsnog bestraald kon worden), versus 25% in de groep die uitwendige radiotherapie had ondergaan na de operatie. 10-jaars overlevingspercentages na een lymfklier recidief in het bekken waren 18% vs. 0%, en na afstandsmetastasen 8% vs. 4%. Deze resultaten geven aan dat behandeling van vaginale recidieven effectief is met goede genezingskansen, terwijl lymfklier recidieven in het bekken een slechtere uitkomst hebben, vergelijkbaar met afstandsmetastasen.

De rol van moleculaire prognostische factoren voor risicobepaling en indicatiestelling voor adjuvante therapie bij het endometriumcarcinoom.
De resultaten van een pilotstudie die het prognostische belang onderzocht van veranderingen in de voornaamste signaaltransductieroutes (PI3K-AKT, Wnt/β-catenin, microsatelliet-instabiliteit en TP53 mutatie) die betrokken zijn bij de carcinogenese van het endometrioide type endometriumcarcinoom, worden beschreven in **hoofdstuk 7**.
Paraffine blokjes met in formaline gefixeerd tumormateriaal van 65 geselecteerde patiënten die in de PORTEC-2 trial hadden deelgenomen werden geanalyseerd. P53 expressie en microsatelliet-instabiliteit waren de sterkste individuele moleculaire prognostische factoren voor een lagere kans op ziektevrije overleving, terwijl sterke PI3K-AKT signaaltransductie een trend voor een lagere ziektevrije overleving liet zien en β-catenine geen prognostisch effect liet zien. Echter, de combinatie van meerdere geactiveerde signaaltransductieroutes was de sterkste onafhankelijke prognostische factor voor een lagere kans op ziektevrije overleving. Activatie van meerdere signaaltransductieroutes werd gevonden in 8% van de patiënten en was sterk geassocieerd met een agressief ziektebeloop. In tegenstelling tot deze groep hadden de 40% patiënten zonder een verandering in de onderzochte signaaltransductieroutes een zeer lage kans op ziekteprogressie. Deze resultaten geven aan dat moleculaire prognostische factoren gebruikt kunnen worden om het huidige systeem voor risicoclassificatie te verfijnen, en zo in de toekomst tot een verdere afname van zowel over- als onderbehandeling kunnen leiden, door een meer individuele risicovoorspelling en therapiebepaling.

Discussie

Hoofdstuk 8 bespreekt de voornaamste bevindingen van de studies die in dit proefschrift worden gepresenteerd, inclusief een toekomstvisie voor de behandeling van en onderzoek naar endometriumcarcinoom. De 15-jaars resultaten van de PORTEC-1 trial bevestigden het belang van de hoog-intermediaire risicofactoren leeftijd, graad en myometriuminvasie, die bij ongeveer 30% van de endometriumcarcinoom patiënten aanwezig zijn. Uitwendige bestraling leidt tot een belangrijke reductie in het risico op een

locoregionaal recidief (met name door het voorkomen van vaginale recidieven), zonder dat dit leidt tot overlevingswinst vergeleken met geen aanvullende behandeling na de operatie. De PORTEC-2 trial heeft laten zien dat uitwendige radiotherapie en vaginale brachytherapie beide tot een zeer laag risico op een vaginaal recidief leiden, met gelijke overlevingskansen. Tegelijkertijd had vaginale brachytherapie duidelijk gunstigere uitkomsten met betrekking tot behandelingsgerelateerde morbiditeit en kwaliteit van leven, zonder verslechtering ten opzichte van een leeftijdsgecontroleerde normpopulatie. Het is duidelijk geworden dat uitwendige radiotherapie geassocieerd is met lange termijn darmklachten die een impact kunnen hebben op het dagelijks leven en lichamelijk functioneren bij een kwart van de (ex-)patiënten, zelfs 10-15 jaar na de behandeling. Vaginale brachytherapie is derhalve de huidige behandeling van keuze voor patiënten met hoog-intermediaire risicofactoren.
Men kan stellen dat vaginale brachytherapie nog steeds overbehandeling is, omdat ongeveer 7 patiënten met hoog-intermediaire risicofactoren vaginale brachytherapie moeten ondergaan om 1 recidief te voorkomen, terwijl postoperatieve radiotherapie niet leidt tot een verbetering in de overlevingskans. Indien voor geen aanvullende behandeling na de operatie wordt gekozen, worden alleen de 20% patiënten die een recidief ontwikkelen blootgesteld aan radiotherapie, meestal een combinatie van uitwendige radiotherapie en vaginale brachytherapie, wat meer morbiditeit en impact op de kwaliteit van leven heeft dan vaginale brachytherapie alleen. Om de vraag te beantwoorden of een afwachtend beleid beter is dan vaginale brachytherapie na de operatie, wat betreft de uiteindelijke uitkomst, vermindering van overbehandeling, gezondheidsimpact en kosten, is de PORTEC-4 trial geïnitieerd. In PORTEC-4 trial worden endometriumcarcinoom patiënten met hoog-intermediare risicofactoren gerandomiseerd (2:1) tussen vaginale brachytherapie of geen aanvullende behandeling na de operatie. Daarnaast worden de patiënten in de vaginale brachytherapie groep gerandomiseerd (1:1) tussen de standaard dosis van 21 Gy in 3 fracties van 7 Gy of een lager dosisniveau (3 fracties van 5 Gy), om de vraag te beantwoorden of een lagere dosis even effectief is vergeleken met de standaard dosis.

Uitwendige radiotherapie is tegenwoordig alleen nog geïndiceerd voor 15% van de endometriumcarcinoom patiënten met hoog risico kenmerken. Lopende trials (PORTEC-3, GOG#249 en GOG#258) onderzoeken de rol van chemotherapie en de combinatie van chemotherapie met radiotherapie voor deze patiënten.

Een andere manier om over- en onderbehandeling van endometriumcarcinoom te verminderen is het integreren van nieuwe moleculaire prognostische factoren in het huidige systeem van risicoclassificatie, dat gebaseerd is op klinisch-pathologische factoren. De pilotstudie in 65 geselecteerde PORTEC-2 patiënten liet zien dat P53 expressie en microsatelliet-instabiliteit de sterkste individuele genetische prognostische factoren waren. Echter, de combinatie van multipele geactiveerde signaaltransductieroutes was de sterkste onafhankelijke ongunstige prognostische factor met een lagere ziektevrije overleving. Deze bevindingen zullen in een grote groep patiënten gevalideerd moeten worden. Voor dit doel zijn studies gepland die gebruik zullen maken van het tumormateriaal van patiënten uit de PORTEC-1 en PORTEC-2 trial. Daarnaast zal een toekomstige analyse van het tumormateriaal uit de PORTEC-3 trial inzicht geven in moleculaire veranderingen die het gedrag van hoog-risico endometriumcarcinoom bepalen, en factoren die de respons op chemotherapie kunnen voorspellen, zowel voor endometrioide als non-endometrioide tumoren, en mogelijk ook leiden tot toepassing van nieuwe (doelgerichte) middelen.

In de nabije toekomst zullen verbeteringen in de techniek van beeldgestuurde radiotherapie leiden tot een verdere afname van behandelingsgerelateerde morbiditeit. Hiernaast zal door het gebruik van moleculaire prognostische factoren het individuele risico op recidief beter ingeschat kunnen worden. Hierdoor kan de afweging voor behandeling met radiotherapie, rekening houdend met de individuele voorkeuren van de patiënt, beter worden gemaakt. Dit zal er toe leiden dat minder laag risico patiënten worden blootgesteld aan onnodige behandelingsgerelateerde morbiditeit, en dat de behandelingsuitkomsten bij hoog risico patiënten verder kunnen worden verbeterd.

PORTEC participating Radiation Oncology institutions

PORTEC-1:

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Catharina Hospital Eindhoven: M.L.M. Lybeert
Medisch Spectrum Twente Enschede: J.J. Jobsen, J.H. Meerwaldt
University Medical Center Utrecht: C.C. Wárlám-Rodenhuis
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MAASTRO Clinic, Maastricht: L.C.H.W. Lutgens
University Hospital Groningen: A.C.M. van den Bergh, E. Pras
Radiotherapy Institute Arnhem: E.M. v.d. Steen-Banasik
Radiotherapy Institute Deventer: M.C. Stenfert Kroese
University Medical Center Radboud, Nijmegen: L.A.M. Pop
University Medical Center Amsterdam: L. Uitterhoeve
Leiden University Medical Center: A.A. Snijders-Keilholz, R.A. Nout
Netherlands Cancer Institute Amsterdam: B.N.F.M. van Bunningen
Westeinde Hospital The Hague: J.H. Biesta
Leyenburg Hospital The Hague: F.M. Gescher
Reinier de Graaf Hospital Delft: J. Pomp
VU Medical Center Amsterdam: O.W.M. Meijer
Radiotherapy Institute Vlissingen: J.H. Tabak
Radiotherapy Institute Leeuwarden: A. Slot

PORTEC-2:

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Curriculum Vitae

Remi Nout werd op 14 januari 1975 geboren in Ilesha, Nigeria. In 1993 behaalde hij het VWO diploma op het Christelijk Streek Lyceum in Ede. In dat jaar startte hij met de studie geneeskunde aan de Universiteit Maastricht. Na het volgen van een wetenschapsstage bij de afdeling huisartsgeneeskunde van de University of British Columbia, Canada (begeleider Dr. S. Grzybowski) behaalde hij in 1997 zijn doctoraal examen. Na een klinische stage van drie maanden in het Moi University Hospital in Eldoret, Kenya, behaalde hij in 2000 zijn artsexamen. Op zoek naar het juiste specialisme werkte hij achtereenvolgens als arts-assistent op de afdelingen spoedeisende hulp en orthopedie in het Laurentius Ziekenhuis in Roermond, als arts-assistent psychiatrie bij de crisisdienst van Mentrum in Amsterdam en volgde hij gedeeltelijk de opleiding tot huisarts aan het Academisch Medisch Centrum te Amsterdam.

In 2003 begon hij met de opleiding tot radiotherapeut-oncoloog in het Leids Universitair Medisch Centrum (opleider: prof. dr. E.M. Noordijk). Tijdens zijn opleiding startte hij in 2007 met het onderzoek naar de uitkomsten van de PORTEC-2 trial en kwaliteit van leven studies. Sinds het voltooien van zijn opleiding in 2008 is hij als radiotherapeut-oncoloog werkzaam in het Leids Universitair Medisch Centrum, met als aandachtsgebieden gynaecologische oncologie en bot- en wekedelentumoren. Deze klinische werkzaamheden combineert hij met het werk als onderzoeker, o.a. voor de PORTEC trials en in het EMBRACE netwerk.

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