1

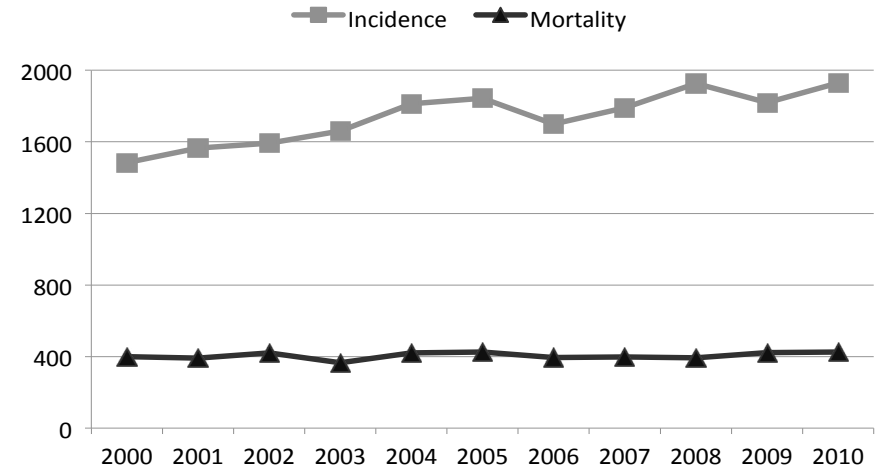
Introduction

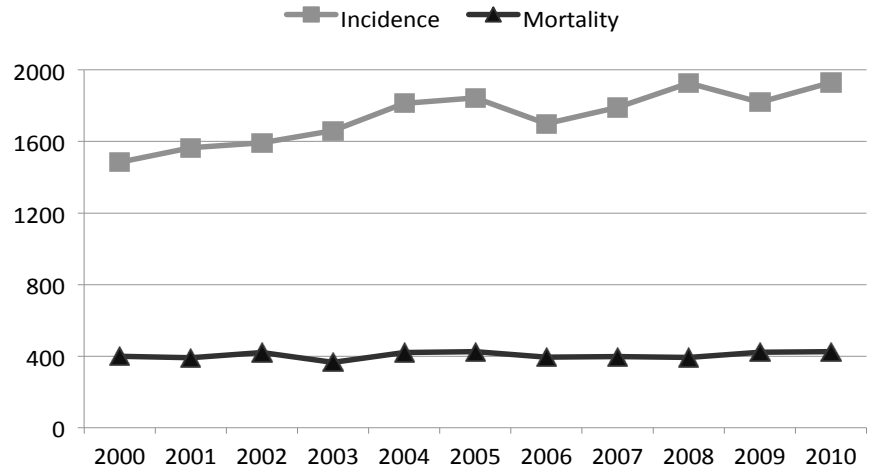
1.1 Epidemiology of endometrial cancer

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]





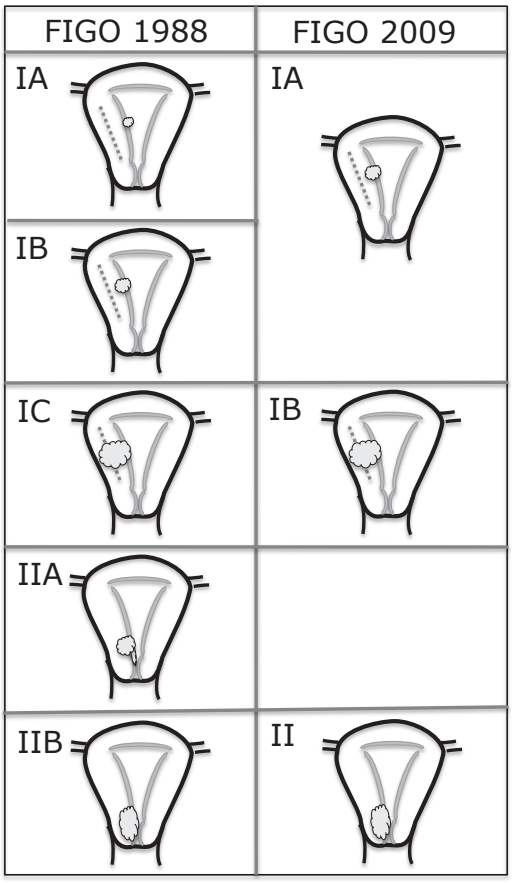


Figure 2.

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

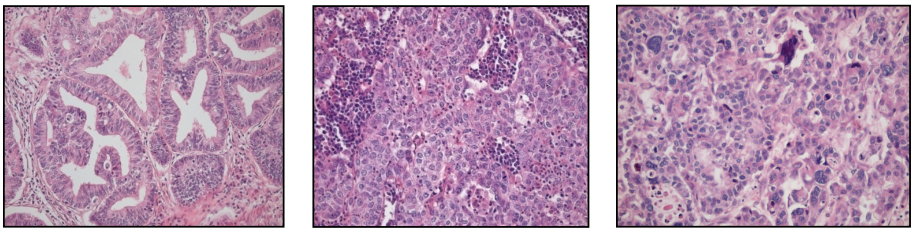
FIGO 2009 staging
IA: <50% myometrial invasion;
IB: >50% myometrial invasion
II: invasion of the cervical stroma;
IIIA: Tumor invades the serosa of the corpus uteri and/or adnexae
IIIB: Vaginal and/or parametrial involvement
IIIC: Metastasis to pelvic (C1) and/or para-aortic (C2) lymph nodes
IVA: Tumor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

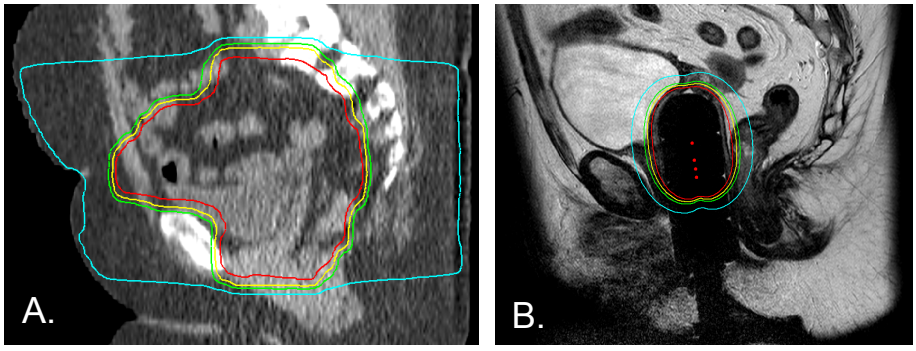


Figure 4. (A) Pelvic external beam radiotherapy dose distribution on CT in the sagittal midplane, in red 95% isodose of 46 Gy. (B) Vaginal brachytherapy using a 3.5 cm vaginal cylinder, dose distribution on MRI in the sagittal midplane, in red 100% isodose of 7 Gy at 0.5 cm distance of the applicator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

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