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

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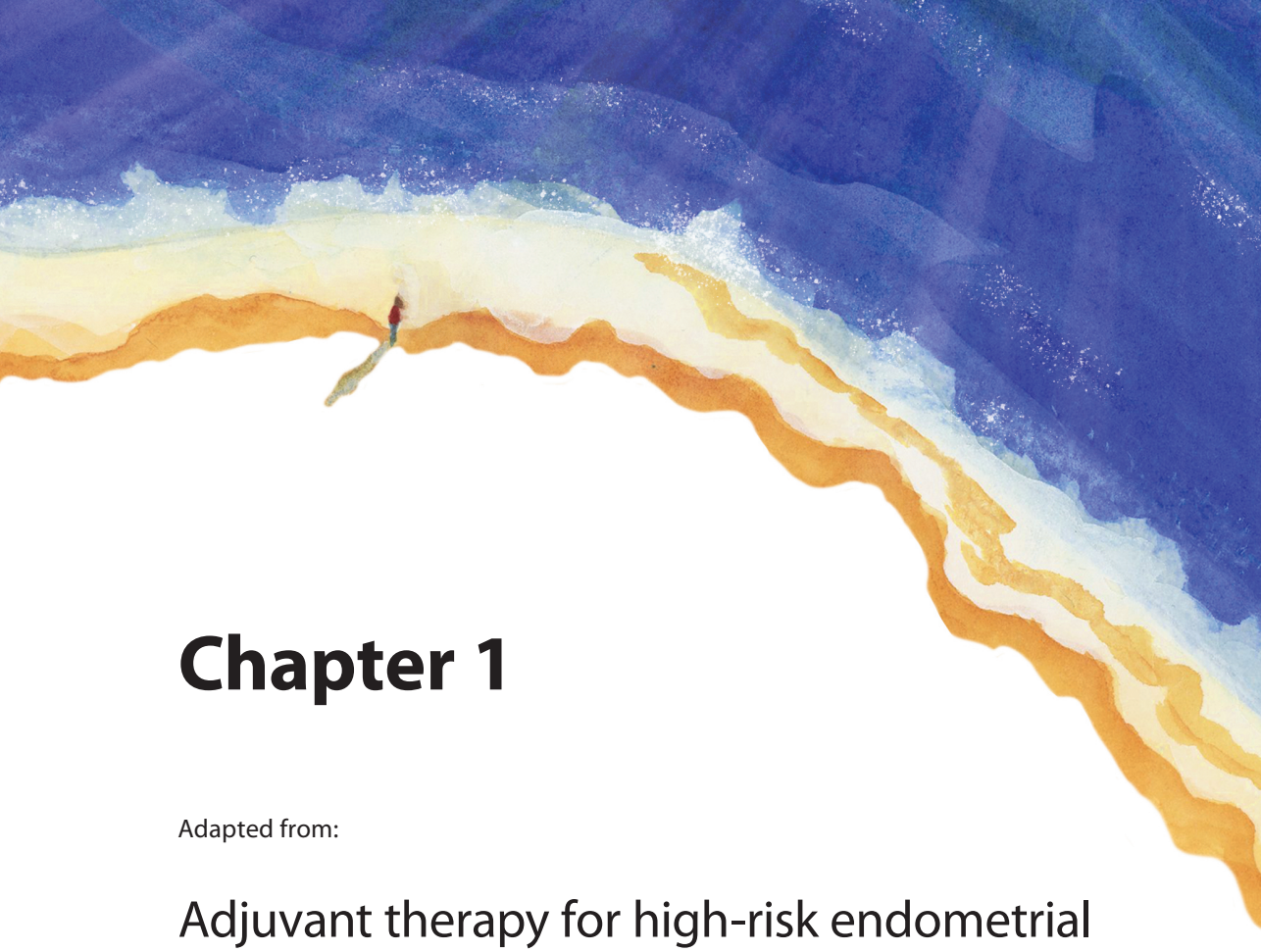

Chapter 1

Adapted from:

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

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1. INTRODUCTION

1.1 Epidemiology of endometrial cancer

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

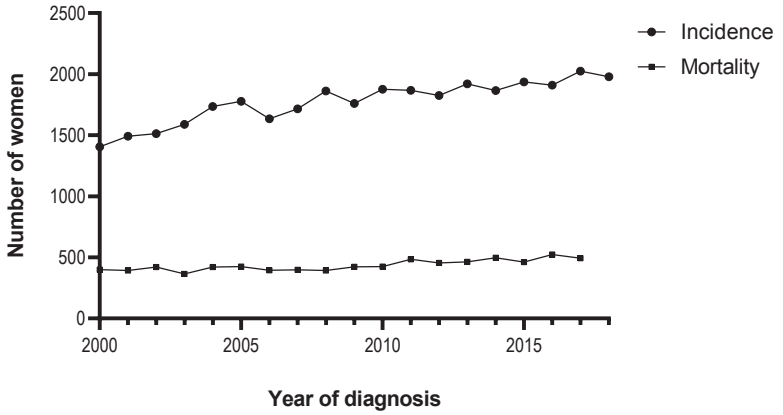

Figure 1. Netherlands Cancer Registry: incidence and mortality of endometrial cancer in the Netherlands between 2000 and 2018[4]

1.2 Surgery

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

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

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

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

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

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

1.3 Risk classification

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

FIGO stage

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

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

Stage	Description
Stage I	Tumour confined to corpus uteri
IA	No or less than half myometrial invasion
IB	More than half myometrial invasion
Stage II	Tumor invades cervical stroma, but does not extend beyond the uterus
Stage III	Local and/or regional spread of the tumor
IIIA	Tumor invades the serosa and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	Positive pelvic nodes
IIIC2	Positive para-aortic nodes with or without positive pelvic nodes
Stage IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Invasion of bladder/bowel mucosa
IVB	Distant metastasis, including intra-abdominal metastases and/or inguinal lymph nodes

Histological type and grade

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

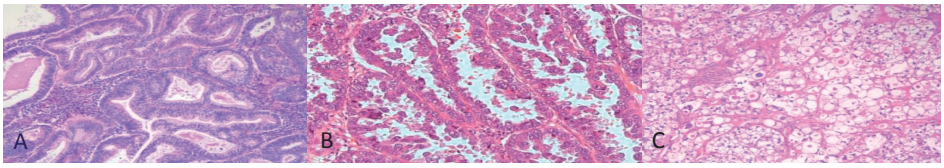

Figure 2. Hematoxyline-eosine (HE) coupes: endometrioid (A), serous (B) and clear cell (C) endometrial cancer

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

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

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

1.4 Pathology assessment

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

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

1.5. Adjuvant treatment

Low-intermediate risk endometrial cancer

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

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

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

Abbreviations: LVSI; lymph-vascular space invasion

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

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

High-risk endometrial cancer

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

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

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

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

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

In an Italian trial[33], 345 patients with high-risk endometrial cancer were randomised to EBRT or five cycles of cyclophosphamide 600 mg/m2, doxorubicin 45 mg/m2 and cisplatin 50mg/m2 (CAP) chemotherapy every 4 weeks. Sixty-five percent of patients had stage III disease and 56% of patients had a grade 3 endometrioid tumour. EBRT delayed pelvic recurrence and chemotherapy delayed distant metastases, but no differences in overall and progression-free survival were found: 5-year overall survival was 69% (EBRT) vs. 66% (CAP) and 5- year progression-free survival was 63% vs. 63%. In these two trials, only women with endometrioid tumours were included.
In the GOG-122 trial[35], patients with advanced stage disease (stage III and IV endometrial cancer, residual macroscopic disease ≤2 cm allowed) were randomised to receive whole-abdominal irradiation (WAI) or chemotherapy (eight cycles of doxorubicin 60mg/m2 and cisplatin 50 mg/m2). Chemotherapy significantly improved overall survival (55% vs. 42%). However, event rates were similar (54 vs. 50%) and 5- year rates of pelvic recurrence were 18% for chemotherapy and 13% for RT. Substantial grade 3–4 toxicity occurred in patients treated with chemotherapy, and significantly higher rates of peripheral neuropathy were reported after treatment by patients treated with chemotherapy.[51]
Relatively large multicenter and single center retrospective studies reported higher rates of pelvic recurrence if high-risk patients were treated without radiotherapy supporting the continued use of locoregional radiotherapy in patients undergoing adjuvant chemotherapy.[52-54] In a phase II trial (RTOG 9708) among women with high-risk endometrial cancer, the combination of EBRT with two concurrent cycles of cisplatin 50 mg/m2 on days 1 and 28, followed by four adjuvant cycles of cisplatin 50 mg/m2 and paclitaxel 175 mg/m2 was tested in 46 patients, resulting in favourable 4-year overall and disease-free survival rates of 85% and 81%, respectively.[55] A completion rate of 98% was reported. Acute grade 3 and grade 4 adverse events were reported in 12 (27%) and 1 (2%) patient during concurrent chemotherapy, respectively, and in 9 (21%) and 26 (62%) patients during adjuvant chemotherapy. Chronic grade 3 and 4 adverse events were reported in 7 patients (16%) and 1 patient (2%).[56]

1.6 Toxicity and health-related quality of life

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

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

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

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

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

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

1.7 Aims and outline of this thesis

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

The aims of this thesis were:

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

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

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