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

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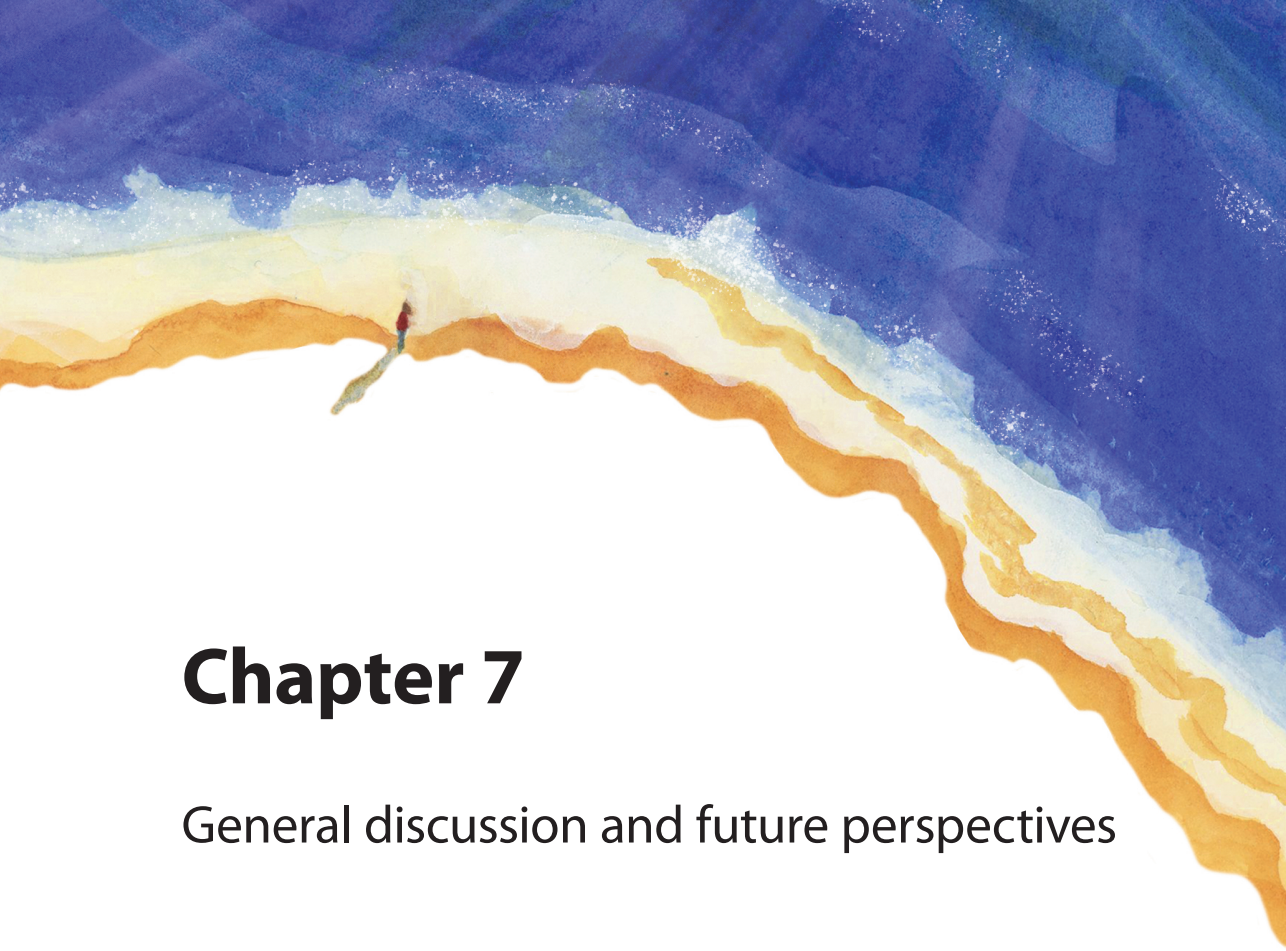

Chapter 7

General discussion and future perspectives

7. GENERAL DISCUSSION AND FUTURE PERSPECTIVES

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

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

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

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

7.1. Adjuvant treatment for high-risk endometrial cancer

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

7.1.1. Efficacy of adjuvant treatment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7.1.2. Adverse events and health-related quality of life

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

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

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

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

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

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

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

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

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

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

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

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

7.1.3. Upfront pathology review

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

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

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

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

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

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

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

7.2.1. Which patients benefit from chemotherapy?

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

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

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

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

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

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

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

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

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

7.2.3. Integration of molecular characteristics in the risk classification

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

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

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

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

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

7.3 Future perspectives

7.3.1. Implementation of molecular characteristics into the clinic

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

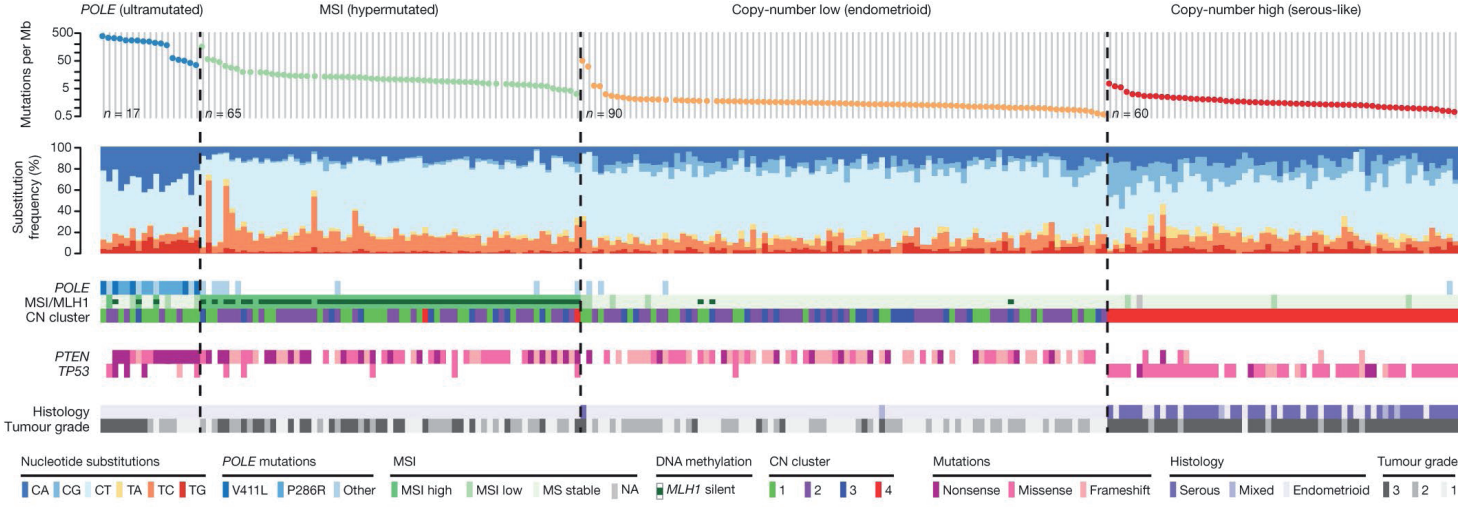

Figure 1. Molecular characterization of endometrial cancer proposed by the Cancer Genome Atlas Group[47]

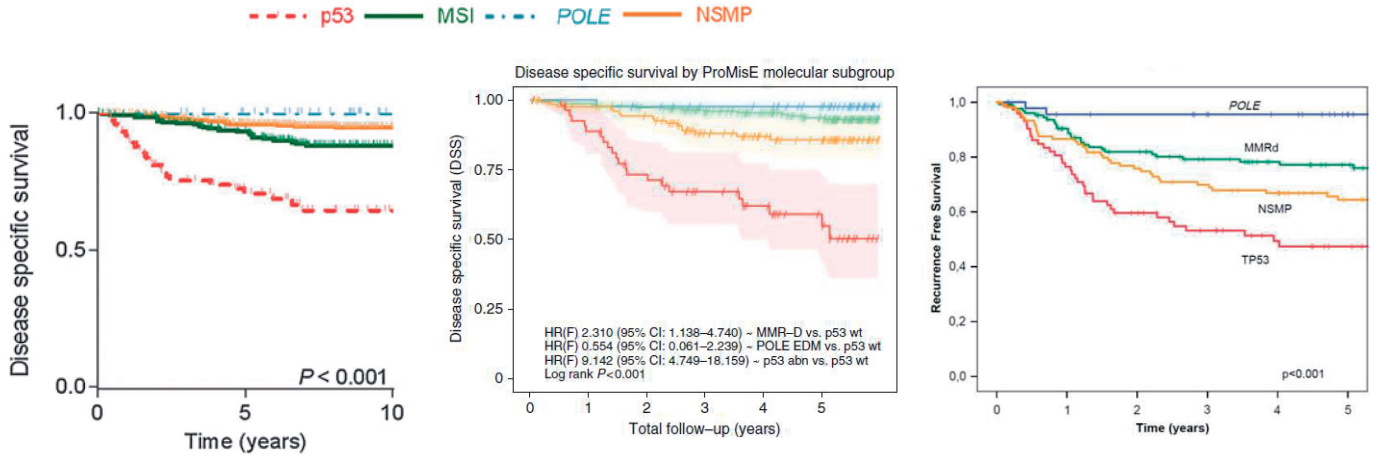

Figure 2. Prognostic significance of the TCGA subgroups in: (A) low-intermediate risk endometrial cancer in the PORTEC 1 and 2 trial[42]; (B) in an unselected retrospective German cohort (validation cohort of ProMisE)[50] and in (C) an international cohort of endometrioid grade 3 tumours.[54]

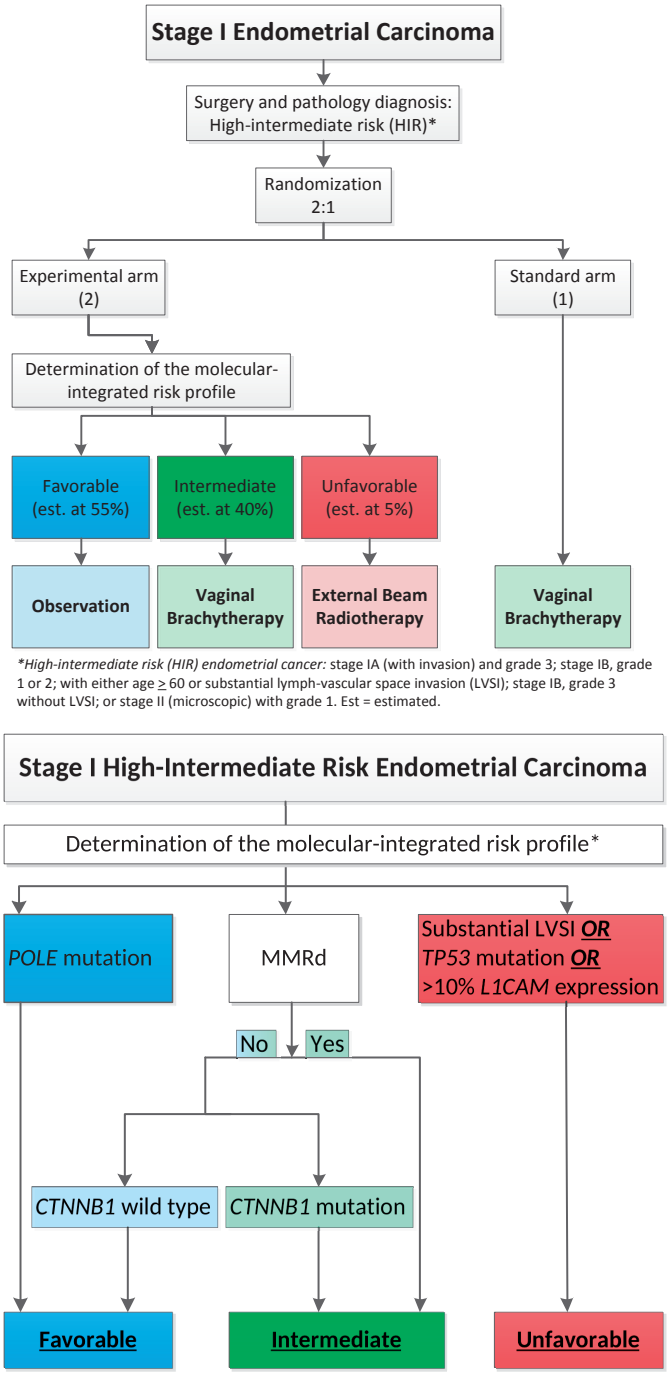

Figure 3. PORTEC-4A trial design (A) and decision tree of the molecular-integrated risk profile (B).[53]

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

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

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

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

7.3.2. Improvement of radiation techniques

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

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

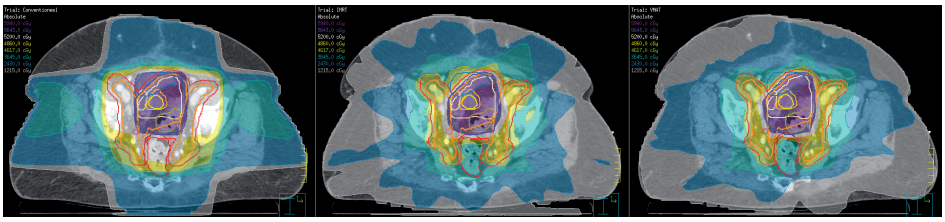

Figure 4. Examples of dose distributions of pelvic external beam radiotherapy for three different radiation techniques (A) 3-dimensional conformal radiotherapy, (B) intensity modulated radiotherapy and (C) volumetric modulated arc therapy.

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

7.4. Shared decision making

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

7.5. Conclusion

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

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

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

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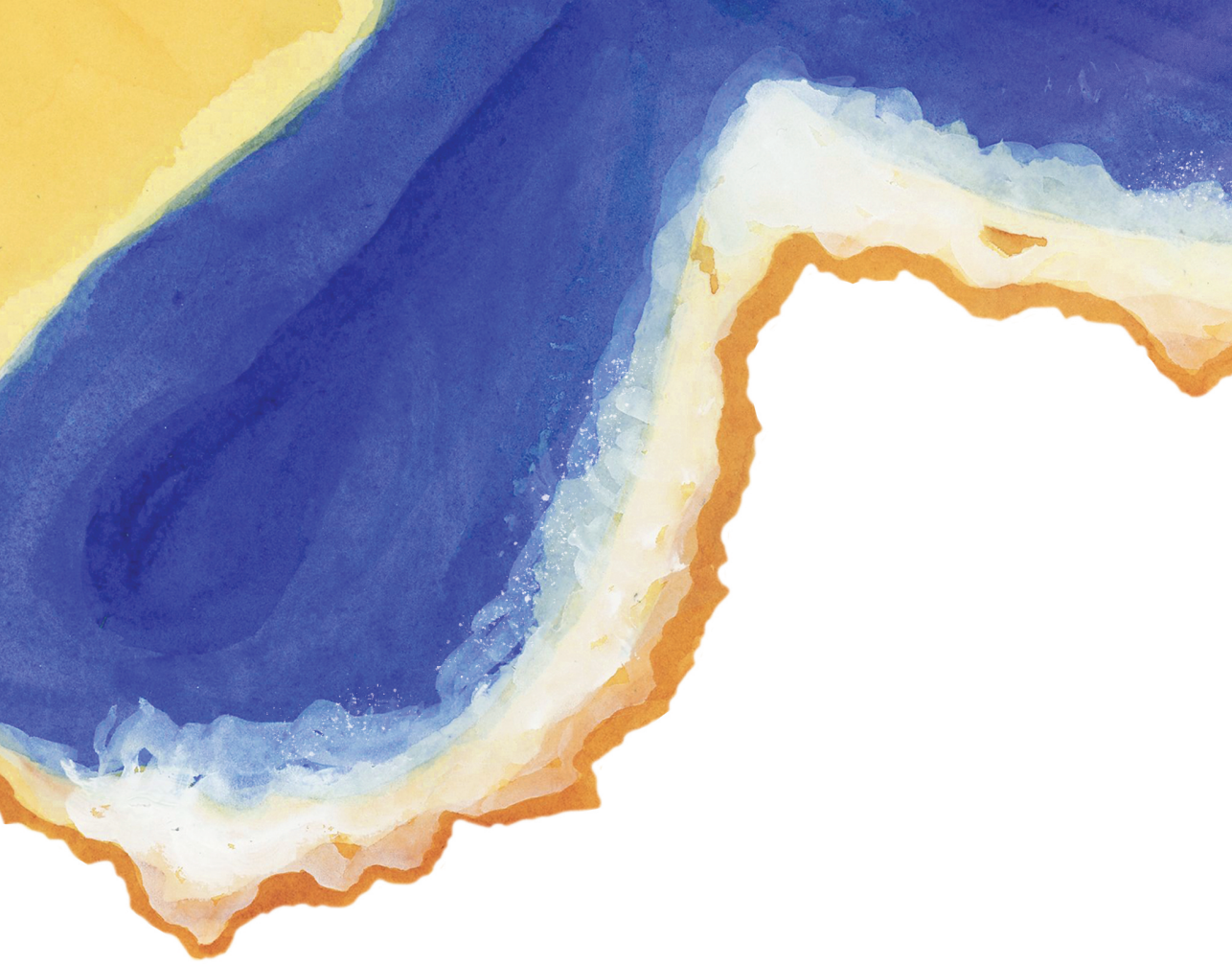

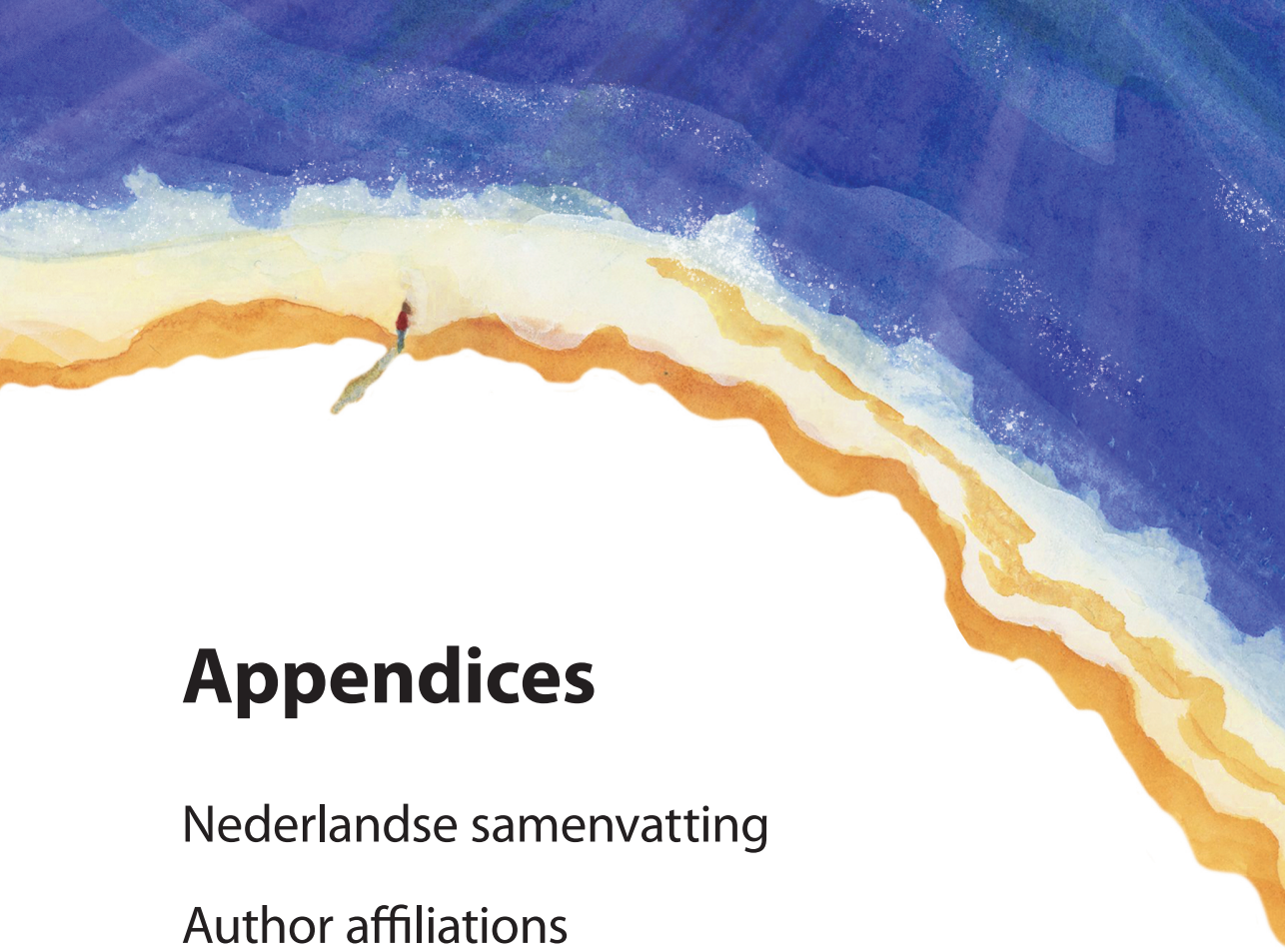

Appendices

Nederlandse samenvatting

Author affiliations

PORTEC-3 participating groups and centres

List of publications and conference presentations

Curriculum Vitae

Dankwoord