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Towards personalized treatment for high risk endometrial cancer

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Chapter 1

General introduction

1.1 Epidemiology of endometrial cancer

Endometrial cancer is the most common gynecological cancer in developed countries. It primarily affects postmenopausal women aged between 60 and 85 years. The major risk factors for developing endometrial cancer are obesity, diabetes, early age at menarche, nulliparity, late-onset menopause, older age, and prolonged use of tamoxifen,[1] which are mainly associated with prolonged and/or unopposed exposure to estrogens. The incidence of endometrial cancer has been gradually rising over the past decades, which is attributed to ageing of the population and increased rates of obesity. The average annual age-adjusted incidence rate of endometrial cancers was 15.3 per 100.000 women in the Netherlands (European standardized rate) and 28.1 per 100.000 women in the United States (2000 U.S. standard population; both based on 2014-2018 cases). Mortality was 2.2 and 5.0 per 100.000 women per year, respectively (based on 2015-2019 deaths).[2, 3] Incidence rates in the United States are higher, mainly due to the higher prevalence of obesity. In addition, the rate of non-endometrioid histologies is higher, especially among Afro-American women, resulting in higher mortality rates.[3] The majority of women diagnosed with endometrial cancer have a favorable prognosis since they present with early-stage disease (stage I and II, confined to the uterus) due to early symptoms of vaginal bleeding. However, prognosis strongly depends on stage at diagnosis, and those with advanced or metastatic disease have a poor prognosis.[3]

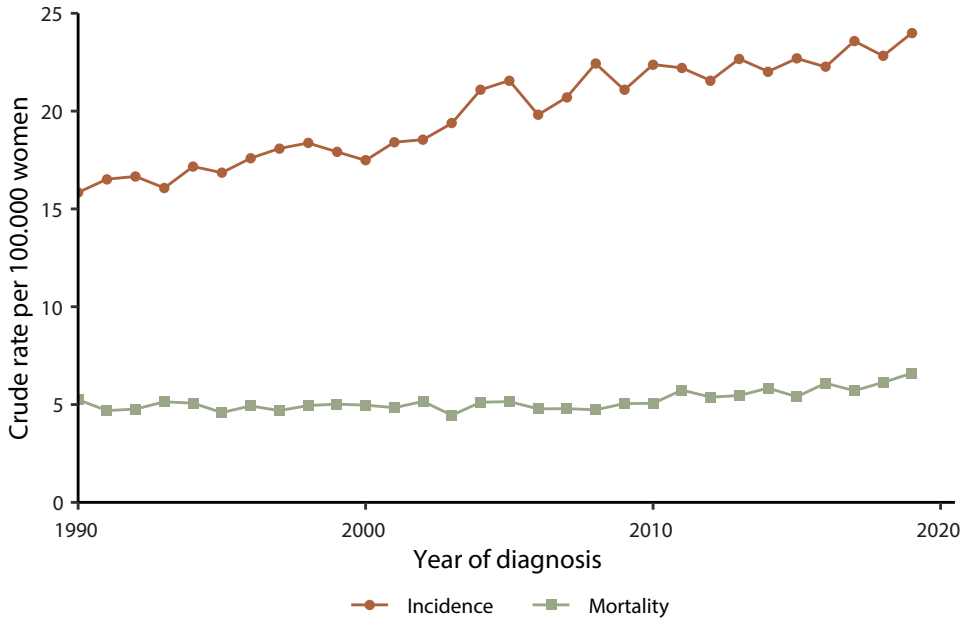

Figure 1. Netherlands Cancer Registry: Increasing crude incidence and mortality of endometrial cancer in the Netherlands between 1990 and 2019[2]

1.2 Endometrial cancer classification

Risk factors have been identified to distinguish categories for risk of recurrence and facilitate recommendations on adjuvant treatment. The prognostic risk stratification of endometrial cancer has evolved. Importantly, a transformation from the morphology-based classification towards an integrated model based on histologic and molecular features has been induced by the four molecular subclasses first described by The Cancer Genome Atlas (TCGA).[4] The most recent risk classification is based on the extent of disease (stage), histopathologic features and the molecular subclass of the tumor.[5]

1.2.1 FIGO staging

The current International Federation of Gynecology and Obstetrics (FIGO) staging was published in 2009. Definitive staging is based on surgical and pathology findings, taking into account the extent of the tumor and presence of (lymph node) metastases (Table 1). This staging system has high prognostic value; five-year overall survival for stage IA endometrial cancer is about 95%, for stage IIIC 70% and for stage IVB 18%.[3]

Table 1. Endometrial cancer FIGO 2009 staging[6]

I	**Tumor confined to the corpus uteri**
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
II	**Tumor invades cervical stroma, but does not extend beyond the uterus***
III	**Local and/or regional spread of the tumor**
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexa
IIIB	Vaginal involvement 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 lymph nodes
IV	**Tumor invades bladder and/or bowel mucosa, and/or distant metastases**
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastasis, including intra-abdominal metastases and/or inguinal nodes

*Endocervical glandular involvement only should be considered as Stage I

1.2.2 Traditional classification and histological features

Since the 1970s, endometrial cancers have traditionally been classified into two categories based on clinical, metabolic and endocrine features.[7] Type I tumors are mostly estrogen-dependent low grade endometrioid cancers, which occur in relatively young women at perimenopausal or postmenopausal ages. Type II tumors are predominantly non-endometrioid tumors among elderly women, associated with worse outcomes. However, many cancers fall outside this simple dichotomous classification with significant overlap between the two types and heterogeneity with respect to clinical, biological, genetic and pathological features.

Histologically, the most common subtype is endometrioid carcinoma (≥75%). Non-endometrioid histological types are mainly serous endometrial carcinoma, clear cell carcinoma, uterine carcinosarcoma and un/dedifferentiated carcinoma. Endometrioid endometrial cancers are graded as low (grade 1 and 2) or high-grade (grade 3, poorly differentiated) according to FIGO grading,[8] whereas all other histologic subtypes are considered high-grade by definition.

Age, stage, and pathological features as depth of myometrial invasion, histopathologic type and FIGO grade, have consistently shown to be of prognostic value for risk of recurrence, metastases and survival for patients with endometrial cancer. These prognostic factors have been used to define low, intermediate, high-intermediate, and high risk groups, and have been based on data from earlier randomized trials. In addition, lymphovascular space invasion (LVSI) has consistently been demonstrated to be a negative prognostic factor. More recently, the extent of LVSI has shown to be of importance emphasizing the need for a uniform definition and scoring system. Therefore a three-tiered scoring system of LVSI has been defined, distinguishing no, focal or substantial LVSI with moderate to good reproducibility.[9, 10] This scoring system is recommended in the current WHO classification[8] and ESGO/ESTRO/ESP guidelines[5], defining substantial LVSI as 5 or more involved vessels. Regardless of disease stage, substantial LVSI has been shown to be a strong independent prognostic factor and is associated with the presence of nodal disease, disease recurrence and impaired survival, both in presence and absence of nodal disease.[11-14] In the PORTEC-1 and 2 trials, it has shown to predict pelvic recurrence, distant metastasis and overall survival in intermediate risk endometrial cancer.[15] In high risk disease, both with or without documented lymph node metastases, it has shown to predict recurrence and survival.[11, 13, 14]

1.2.3 Molecular classification

The molecular landscape of endometrial cancer was described by TCGA in 2013[4] and has had profound impact on the prognostication of women with endometrial cancer. TCGA distinguished four molecular subgroups based on somatic copy number alterations and tumor mutational burden. These four subgroups include: ultra-mutated endometrial cancers characterized by pathogenic variants in the exonuclease domain of DNA polymerase-epsilon (*POLE*); hyper-mutated endometrial cancers characterized by microsatellite instability (MSI) or mismatch repair deficiency (MMRd); a copy-number high group with frequent *TP53* mutations; and a copy-number low group with a low mutational burden. In the following years, four subgroups similar to those originally described were identified by the use of surrogate markers available in routine clinical practice: *POLE*-ultramutated (*POLE*mut), mismatch repair deficient (MMRd), p53-abnormal (p53abn) and No Specific Molecular Profile (NSMP).[16] Given the presence of multiple molecular classifiers in 3 to 6% of endometrial cancers[17], molecularly based stratification can only be performed if there is simultaneous assessment of p53, MMR, and *POLE* status according to the WHO diagnostic algorithm (Figure 2). Using this approach, the molecular endometrial cancer classification has demonstrated to have a strong prognostic value in clinical trials and unselected cohorts of both low-intermediate risk and high risk early-stage endometrial cancer.[18-21] Recently, the molecular groups have been integrated into the WHO classification system 2020[8] and treatment guidelines[5].

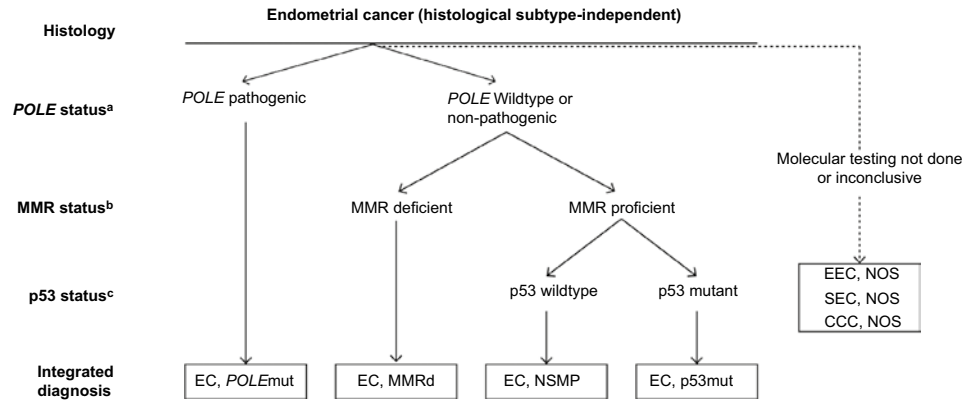

Figure 2. Diagnostic algorithm for the integrated histomolecular endometrial cancer classification[8]
EC = endometrial cancer; MMR = mismatch repair; MMRd = mismatch repair-deficient; NSMP = no specific molecular profile.
[a]Pathogenic *POLE* variants include p.Pro286Arg, p.Val411Leu, p.Ala456Pro, p.Ser459Phe and p.Pro436Arg.
[b]MMR deficiency is defined by loss of one or more MMR proteins (MLH1, PMS2, MSH2, and MSH6).
[c]P53 immunohistochemistry is an acceptable surrogate marker for *TP53* mutation status in MMR-proficient, *POLE*-wildtype EC.

For adjuvant treatment recommendations, the molecular classification seems to be particularly relevant in the context of high risk endometrial cancers. Even within this seemingly unfavorable group, there is a group of patients with an excellent prognosis: the *POLE*mut tumors and a group with a poor prognosis: the p53abn tumors. The MMRd and NSMP tumors have an intermediate prognosis.[21]

Testing for MMR status has been shown to predict the efficacy of checkpoint inhibition therapy.[22-24] In addition, MMR immunohistochemistry can be used as screening methodology to identify patients who may have Lynch syndrome. The majority of MMRd endometrial cancer is caused by hypermethylation of the *MLH1* promoter region, but a small proportion is caused by Lynch syndrome (encompassing an estimated 3% of all endometrial cancers). Lynch syndrome is a highly penetrant, hereditary cancer syndrome caused by germline variants in one of the four DNA mismatch repair genes: mutL homologue 1 (*MLH1*), mutS homologue 2 (*MSH2*), mutS homologue 6 (*MSH6*), or postmeiotic segregation increased 2 (*PMS2*). Lynch syndrome associated tumors arise following MMRd due to the somatic inactivation of the remaining wildtype MMR allele. MMRd leads to the accumulation of mismatches, insertions, and deletions in repeated sequences, also known as MSI. Endometrial cancer is often the first malignancy affecting women with Lynch syndrome,[25] and their risk of metachronous cancer is approximately 24% at 10 years.[26] The identification of Lynch syndrome in patients who present with endometrial cancer as their first malignancy is of essential value for counselling and cancer surveillance for both the patient and her family.

1.2.4 Prognostic risk classification

The definitions of the prognostic risk groups have changed over time and have mostly originated from large clinical trials. Most patients present with low-risk or intermediate-risk disease. However, about 15% of patients present with high risk disease comprising early-stage endometrial cancer with high risk features (most notably grade 3, substantial LVSI, non-endometrioid histology, cervical stromal involvement) and FIGO stage III disease. The prognostic relevance of the molecular classification has led to major modification of the risk groups as previously defined in the ESMO-ESGO-ESTRO consensus[27] into an updated risk classification in the 2020 ESGO-ESTRO-ESP guideline, which incorporated a risk classification both with and without knowledge of the molecular subgroups[5] (Table 2).

Table 2. Definition of prognostic risk groups following the ESMO-ESGO-ESTRO consensus and ESGO/ESTRO/ESP guidelines

		ESGO/ESTRO/ESP guidelines (2020)[5]	
Risk group	**ESMO-ESGO-ESTRO consensus (2015)[27]**	**Molecular classification unknown**	**Molecular classification known***
Low	Stage I endometrioid, grade 1-2, <50% myometrial invasion, LVSI negative	Stage IA endometrioid + low-grade + LVSI negative or focal	Stage I–II *POLE*mut endometrial carcinoma, no residual disease Stage IA MMRd/NSMP endometrioid carcinoma + low-grade + LVSI negative or focal
Intermediate	Stage I endometrioid, grade 1-2, ≥50% myometrial invasion, LVSI negative	Stage IB endometrioid + low-grade + LVSI negative or focal Stage IA endometrioid + high-grade + LVSI negative or focal Stage IA non-endometrioid without myometrial invasion	Stage IB MMRd/NSMP endometrioid carcinoma + low-grade + LVSI negative or focal Stage IA MMRd/NSMP endometrioid carcinoma + high-grade + LVSI negative or focal Stage IA p53abn and/or non-endometrioid without myometrial invasion
High–intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status	Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion Stage IB endometrioid high-grade regardless of LVSI status Stage II	Stage I MMRd/NSMP endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion Stage IB MMRd/NSMP endometrioid carcinoma high-grade regardless of LVSI Stage II MMRd/NSMP endometrioid carcinoma
High	Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status Stage II Stage III endometrioid, no residual disease Non-endometrioid	Stage III–IVA with no residual disease Stage I–IVA non-endometrioid with myometrial invasion, and with no residual disease	Stage III–IVA MMRd/NSMP endometrioid carcinoma with no residual disease Stage I–IVA p53abn endometrial carcinoma with myometrial invasion, with no residual disease Stage I–IVA NSMP/MMRd serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	Advanced: Stage III residual disease and stage IVA Metastatic: IVB	Stage III–IVA with residual disease Stage IVB	Stage III–IVA with residual disease of any molecular type Stage IVB of any molecular type

*For stage III–IVA *POLE*mut endometrial cancer and stage I–IVA MMRd or NSMP clear cell cancer with myometrial invasion, insufficient data are available to allocate these patients to a prognostic risk group in the molecular classification.

LVSI = lymphovascular space invasion; MMRd = mismatch repair deficient; NSMP = non-specific molecular profile; non-endometrioid = serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed; p53abn = p53 abnormal; *POLE*mut = *POLE*-ultramutated.

1.3 Treatment

1.3.1 Surgery in early-stage disease

Standard treatment for early-stage endometrial cancer consists of (laparoscopic) total hysterectomy with bilateral salpingo-oophorectomy. Lymphadenectomy is controversial due to the absence of survival benefit and added toxicity.[28, 29] It is in most guidelines recommended for staging purposes, and sentinel lymph node biopsy with ultra-staging has more recently been shown to be an acceptable alternative.[30]

1.3.2 Adjuvant treatment

Since 1980, multiple large studies have been conducted to elucidate the role of adjuvant treatment in early-stage endometrial cancer. This has led to more individual risk-based adjuvant treatment recommendations based on clinicopathological risk factors, and further refinement is ongoing. The additional value of pelvic external beam radiotherapy has shown to be limited to tumors with high risk features (i.e. grade 3 and deep invasion and/or LVSI, unfavorable histology, unfavorable molecular factors). For early-stage tumors with low to intermediate risk features, treatment has been de-escalated. In case of low-risk endometrial cancer, no adjuvant treatment is recommended since the prognosis is excellent with surgery alone. This is supported by the PORTEC-1, GOG-99 and ASTEC/EN5 trials. Although these trials showed a significant reduction in the rate of locoregional recurrence, no overall survival benefit was found compared to no additional treatment.[31-33] Moreover, in a Swedish trial for low-risk endometrial cancer, overall recurrence and survival rates were similar after vaginal brachytherapy compared to no additional treatment.[34] Without adjuvant radiotherapy, the risk of recurrence is highest in the vaginal vault region. In the case of vaginal relapse, salvage radiotherapy by pelvic radiotherapy and brachytherapy has been shown to be highly effective. The PORTEC-2 trial and Swedish trial among patients with early-stage (high)-intermediate disease[35-37] have shown that vaginal brachytherapy leads to a similarly high local control compared to pelvic radiotherapy, and this became the standard adjuvant treatment for women with high-intermediate risk endometrioid type endometrial cancer.

While adjuvant treatment with pelvic radiotherapy improves vaginal, pelvic and para-aortic nodal control, and thus is indicated for early-stage endometrial cancer with high risk features, adjuvant chemotherapy has been investigated to reduce the risk of distant metastases. Two randomized trials compared both treatment modalities in intermediate or high risk endometrial cancer; Susumu et al. included mainly intermediate risk disease (stage IB and/or low grade), while in the trial of Maggi et al. 66% of the population had stage III disease. In both trials, the pelvic radiotherapy and chemotherapy arms showed similar recurrence-free survival rates.[38, 39]

Subsequently, the combination of chemotherapy and radiotherapy has been investigated. A benefit of combined chemoradiotherapy in comparison with pelvic radiotherapy alone was suggested by the pooled analysis of the NSGO9501-EORTC55991 trial, which mainly included stage I with grade 3 and/or deep myometrial invasion endometrial cancer of endometrioid, serous and clear cell types, and the MaNGO-Iliade III trial which included stage II-III endometrioid type endometrial cancer. Significantly longer progression-free survival (5-year PFS 69% vs 78%, HR 0.63, 95% CI 0.44-0.89; p = .009) and a trend for improved overall survival (5-year OS 75% vs 82%, HR 0.69, 95% CI 0.46-1.03; p = .07) were reported with added platinum-based chemotherapy.[40] The beneficial effect of combined chemoradiotherapy versus pelvic radiotherapy alone was confirmed by the PORTEC-3 trial. The PORTEC-3 trial included patients with stage I grade 3 endometrioid endometrial cancer with myometrial invasion or LVSI; stage II or III endometrioid endometrial cancer; or stage I to III with serous or clear-cell histology. Both progression-free survival (5-year PFS 76% vs 69%, HR 0.70; p = .016) and overall survival (5-year OS 81% vs 76%, HR 0.70; p = .034) were improved after chemoradiotherapy. The highest absolute benefit was seen in patients with serous cancer (19%) and those with stage III disease (10%).[41]

Simultaneously with the PORTEC-3 trial, the role of pelvic radiotherapy for locoregional control of high risk endometrial cancer was investigated in early-stage and more advanced disease. In stage I-II tumors, the importance of pelvic radiotherapy was supported by the GOG-249 trial, which showed better pelvic and peri-aortic nodal control 5 years after adjuvant pelvic radiotherapy compared to combined brachytherapy and 3 cycles of carboplatin-paclitaxel chemotherapy (4% vs 9%, HR 0.47, 95% CI 0.24-0.94). Recurrence-free and overall survival were similar in both arms, while chemotherapy induced a higher degree of acute toxicity. There was little difference in late toxicity; however quality of life outcomes showed worse physical functioning at 6 months and more sensory neuropathy in the chemotherapy arm at 24 months.[42] In the more advanced setting (stage III-IVA), adjuvant pelvic radiotherapy combined with chemotherapy was compared to 6 cycles of carboplatin-paclitaxel chemotherapy alone in the GOG-258 trial, which included in majority FIGO Stage IIIC endometrial cancer (few with residual disease). Recurrence-free survival was comparable between the arms (5-year RFS 59% vs 58%, HR 0.90, 90% CI 0.74 -1.10, p = .20), and to the FIGO stage III pelvic radiotherapy alone arm in the PORTEC-3 trial (5-year RFS 58%), but not to the FIGO stage III chemoradiotherapy arm in the PORTEC-3 trial (5-year RFS 71%) which emphasizes the difference in included patients. However, combined chemoradiotherapy reduced the risk of pelvic and peri-aortic nodal relapse compared to chemotherapy alone (11% vs 20%, HR 0.43, 95% CI 0.28-0.55).[43]

1.3.3 Treatment for advanced disease

Treatment in the advanced or recurrent setting should be discussed in a multidisciplinary team on a case-by-case basis, considering fitness and wishes of the patient, extent of disease, and prior treatment. Treatment options for advanced pelvic disease include surgical cytoreduction or definitive radiotherapy with or without neoadjuvant, concurrent or adjuvant systemic therapy.[5] In case of non-localized disease systemic options should be considered. Response to hormonal treatment is seen in up to 55% of the patients with advanced or recurrent low grade, endocrine receptor positive endometrial cancer.[44, 45] For all other patients with recurrent or metastatic endometrial cancer, chemotherapy with carboplatin and paclitaxel is the standard first line treatment. In case of progression after a long platinum-free interval, re-introduction of platinum can be considered. However, objective response rates are limited to about 10-15%. Therefore, with the evolving molecular knowledge, trials with new treatment strategies have been performed and are ongoing. Immunotherapy has shown to be promising in MMRd endometrial cancer. The single arm phase 2 KEYNOTE-158 and GARNET-trial have shown efficacy of the PD-1 inhibitors pembrolizumab and dostarlimab in chemoresistant MMRd endometrial cancer, with objective response rates of 48% and 42%, respectively, with durable responses.[46, 47] The primary results have led to accelerated US Food and Drug Administration (FDA) approval of pembrolizumab (2017) and FDA and European Medicines Agency (EMA) approval of dorstarlimab (2021) for the second-line treatment for MMRd recurrent or advanced endometrial cancer. The combination of pembrolizumab and antiangiogenic agent Lenvatinib received accelerated FDA approval (2019) for MMR-proficient advanced or recurrent endometrial cancer and EMA approval for all patients with advanced or recurrent endometrial cancer who have disease progression on or following treatment with a platinum containing therapy and are not candidates for curative surgery or radiotherapy. This combination has shown an objective response rate of 30% in the KEYNOTE-146/Study 111 and Study-309/KEYNOTE-775 compared to 15% after chemotherapy, and it has demonstrated an improvement of median overall survival from 12.0 months to 17.4 months and median progression-free survival from 11.4 months to 18.3 months.[48, 49] Further research into immunotherapy used as monotherapy or in combination with targeted therapies is discussed in **chapter 5**.

1.4 Toxicity and quality of life

For each patient, the potential benefit of therapy should be weighed against the costs of longer treatment duration, increased toxicity, and influence on short-term and long-term health-related quality of life (HRQOL). Toxicity is most frequent and severe during treatment, but the lower grade persisting toxicities should not be neglected. Acute grade 1 or 2 gastrointestinal toxicity is frequently (>50%) reported after pelvic radiotherapy.[35]

Pelvic radiotherapy is associated with higher risk of long-term grade 1 to 2 urinary urgency and minor incontinence, and gastrointestinal symptoms such as diarrhea and fecal leakage, impacting physical and role functioning.[31] Meanwhile, women treated with vaginal brachytherapy report better HRQOL, similar to that of an age-matched normative population.[50]

In the analysis of short-term toxicity and HRQOL in the PORTEC-3 trial, the addition of chemotherapy to pelvic radiotherapy worsened the toxicity profile with more frequent and more severe adverse events, mainly hematologic, gastrointestinal and neurologic toxicities, and impaired HRQOL during and after chemoradiation. However, rapid recovery was seen; from 12 months onward, there was no between-group difference in grade 3 to 4 toxicity, and grade 2 or higher sensory neuropathy was the main persistent adverse event at 24 months in 10% of patients after chemoradiation.[51]

In the advanced setting, treatment tolerability is of high importance. Hormonal therapy is generally well tolerated with grade 3 or higher adverse events reported in only 1 to 5% of the patients.[52] Chemotherapy is known to have significant treatment-related toxicity with grade 3 or higher adverse events in 73%.[49] For checkpoint inhibition monotherapy, awareness of immune-related adverse events is warranted, although it is generally well-tolerated with grade 3 or higher treatment-related adverse events in about 10 to 20%.[23, 24, 46, 47] The combination of checkpoint inhibition with Lenvatinib is associated with significant treatment-related toxicity. Grade 3 or 4 adverse events occurred in 89% of patients, most commonly hypertension (38%). This led to frequent interruption or dose reductions, and drug discontinuation in 33% of the patients, whereof in 14% of both agents. The reported HRQOL of women who received pembrolizumab and lenvatinib was comparable to the chemotherapy group.[49] Other combinations of checkpoint inhibition with other targeted therapies, such as Poly (ADP-ribose) polymerase (PARP) inhibition, are ongoing and will be discussed in **chapter 5 and 6**.

1.5 Aims and outline of this thesis

The overall aims of this thesis were:

- To evaluate health-related quality of life up to 5 years after chemoradiotherapy compared with pelvic radiotherapy alone in the adjuvant treatment of high risk endometrial cancer in the PORTEC-3 trial;
- To investigate the preferences of patients and clinicians regarding the benefit-risk trade-off of the addition of chemotherapy to adjuvant pelvic radiotherapy;

- To investigate the prevalence and prognosis of Lynch syndrome-associated endometrial cancer among MMRd endometrial cancers;
- To evaluate the role of combined checkpoint inhibition and PARP inhibition in women with metastatic or recurrent endometrial cancer in terms of progression-free survival and toxicity in the DOMEC trial.

Chapter 2 describes the long-term adverse events and patient-reported HRQOL up to 5-years after adjuvant treatment with concurrent chemoradiotherapy or pelvic radiotherapy alone in the PORTEC-3 trial. Subsequently, the actual differences in overall survival and symptoms known from the PORTEC-3 trial were used in a trade-off questionnaire for patients and clinicians. **Chapter 3** presents the participants' considered sufficient benefit to exceed the risks of adding chemotherapy to radiotherapy, and the factors that were considered important and influenced decision making.

The diagnosis of Lynch syndrome in endometrial cancer is crucial for counseling and cancer surveillance of patients and their relatives. Given its relative rarity, the prevalence and prognosis of Lynch syndrome are not well known. In **chapter 4** the prevalence and prognosis of Lynch syndrome-associated endometrial cancer in relation to MMRd endometrial cancer due to *MLH1*-hypermethylation or other causes is investigated in the large combined cohort of the PORTEC-1, -2 and -3 trials. In addition, the value of IHC-based tumor screening for MMRd is evaluated.

In **chapter 5,** we reviewed the literature on checkpoint inhibition and PARP inhibition as monotherapy or combined treatment in recurrent or metastatic endometrial cancer. It presents the rationale for combination therapy with these targeted agents and an overview of the current and future clinical trials that investigate the potential of these agents in recurrent or metastatic endometrial cancer. In **chapter 6**, the (progression-free) survival and toxicity results of the phase 2, multicenter trial of combined Durvalumab with Olaparib in Metastatic or recurrent Endometrial Cancer (DOMEC) are presented.

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 for patients with endometrial cancer.

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Chapter 2

Long-term toxicity and health-related quality of life after adjuvant chemoradiotherapy or radiotherapy alone for high risk endometrial cancer in the randomized PORTEC-3 trial

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ABSTRACT

Purpose

The survival results of the PORTEC-3 trial showed a significant improvement in both overall and failure-free survival with chemoradiotherapy versus pelvic radiotherapy alone. The present analysis was performed to compare long-term adverse events (AE) and health-related quality of life (HRQOL).

Methods and materials

In the study, 660 women with high risk endometrial cancer were randomly assigned to receive chemoradiotherapy (2 concurrent cycles of cisplatin followed by 4 cycles of carboplatin/paclitaxel) or radiotherapy alone. Toxicity was graded using Common Terminology Criteria for Adverse Events, version 3.0. HRQOL was measured using EORTC QLQ-C30 and CX24/OV28 subscales and compared with normative data. An as-treated analysis was performed.

Results

Median follow-up was 74.6 months; 574 (87%) patients were evaluable for HRQOL. At 5 years, grade ≥2 AE were scored for 78 (38%) patients who had received chemoradiotherapy versus 46 (24%) who had received radiotherapy alone (p = .008). Grade 3 AE did not differ significantly between the groups (8% vs 5%; p = .18) at 5 years, and only one new late grade 4 toxicity had been reported. At 3 and 5 years, sensory neuropathy toxicity grade ≥2 persisted after chemoradiotherapy in 6% (vs 0% after radiotherapy; p < .001) and more patients reported significant tingling or numbness at HRQOL (27% vs 8%, p < .001 at 3 years; 24% vs 9%, p = .002 at 5 years). Up to 3 years, more patients who had chemoradiotherapy reported limb weakness (21% vs 5%; p < .001) and lower physical (79 vs 87; p < .001) and role functioning (78 vs 88; p < .001) scores. Both treatment groups reported similar long-term global health/quality of life scores, which were better than those of the normative population.

Conclusions

This study shows a long-lasting, clinically relevant, negative impact of chemoradiotherapy on toxicity and HRQOL, most importantly persistent peripheral sensory neuropathy. Physical and role functioning impairments were seen until 3 years. These long-term data are essential for patient information and shared decision-making regarding adjuvant chemotherapy for high risk endometrial cancer.

Introduction

The majority of endometrial cancers are diagnosed at an early stage, but 15% to 20% of women with endometrial cancer present with high risk disease. These high risk cancers are characterized by higher grade, advanced stage, or non-endometrioid histology. In contrast to the favorable prognosis of most early-stage endometrial cancers, the high risk group has an increased incidence of distant metastases and cancer-related death. Adjuvant pelvic radiotherapy has been the standard of care for these patients to maximize locoregional control;[1] however, chemotherapy could reduce distant metastases.

The randomized PORTEC-3 trial was initiated to evaluate the benefit of combined adjuvant pelvic radiotherapy and chemotherapy versus pelvic radiotherapy alone for women with high risk endometrial cancer. The updated survival analysis of the PORTEC-3 trial showed a significant benefit in 5-year overall survival and failure-free survival with absolute improvement of, respectively, 5% (81% vs 76%, hazard ratio [HR] 0.70; p = .034) and 7% (76% vs 69%, HR 0.70; p = .016) after chemoradiotherapy. Patients with serous cancers and those with stage III disease were shown to benefit most from the addition of chemotherapy (absolute overall survival improvement of 19% and 10%, respectively, and failure-free survival improvement of 12% and 13%).[2] For each individual patient, the potential survival benefit of chemotherapy should be weighed against the costs of longer treatment duration, increased toxicity, and influence on health-related quality of life (HRQOL).

Pelvic radiotherapy is associated with risks of long-term urinary urgency and incontinence, and bowel symptoms such as diarrhea and fecal leakage, as well as lower physical and role functioning.[3,4] In the analysis of short-term toxicity and HRQOL in the PORTEC-3 trial, the addition of chemotherapy was shown to worsen the toxicity profile with more severe adverse events (AE) and impaired HRQOL during and after chemoradiotherapy. However, rapid recovery was seen; from 12 months onward there was no between-group difference in grade 3 to 4 toxicity, and grade 2 or higher sensory neuropathy was the main persistent AE at 24 months in 10% after chemoradiotherapy.[5] Several studies have reported a negative correlation between chemotherapy-induced peripheral neuropathy (CIPN) and physical functioning or HRQOL.[6-11]

The present analysis was performed to establish long-term AE and patient-reported HRQOL for up to 5-year follow-up in women with high risk endometrial cancer treated in the PORTEC-3 trial. The secondary objective was to evaluate whether specific conditions are correlated to HRQOL.

Methods and materials

Patient population and study design

Details of this open-label, multicenter, randomized phase 3 trial have been reported previously.[2,5,12] Briefly, patients were enrolled at 103 centers through 6 clinical trial groups. Patients were eligible if they had high risk endometrial cancer, defined as histologically confirmed International Federation of Gynecology and Obstetrics (FIGO) 2009 stage I endometrioid endometrial cancer grade 3 with myometrial invasion or lymph-vascular space invasion; stage II or III endometrioid endometrial cancer; or stage I to III serous or clear-cell histology. Surgery consisted of hysterectomy with bilateral salpingo-oophorectomy; clinically suspicious pelvic or periaortic lymph nodes were removed, but lymphadenectomy was not mandatory. Patients were randomly assigned (1:1) to receive pelvic radiotherapy (48.6 Gy in 1.8 Gy fractions, with a brachytherapy boost in case of cervical stromal involvement) or chemoradiotherapy (2 cycles of cisplatin 50 mg/m2 in weeks 1 and 4 of radiotherapy, followed by 4 cycles of carboplatin AUC5 and paclitaxel 175 mg/m2 at 3-week intervals). The study was approved by the Dutch Cancer Society and ethics committees of participating groups.

Study outcome measures

A prespecified secondary objective of the PORTEC-3 trial was to assess AE (grade ≥2 irrespective of study treatment, according to Common Terminology Criteria for Adverse Events [CTCAE] version 3.0) and for mild toxicities (grade 1) HRQOL using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), the cervix 24 (CX24) module, and added neuropathy subscale and other chemotherapy side effect subscale items from the ovarian 28 (OV28) module.[13,14] These were used because the EORTC endometrial module was not yet available at the time of study design. HRQOL questionnaires were completed at baseline (after surgery), after radiotherapy, and at 6, 12, 18, 24, 36, and 60 months from randomization and were discontinued upon diagnosis of recurrence or death. For all items, Likert-type response scales were used ranging from 4 to 7 points. Higher scores on functional and global HRQOL scales represented better levels of functioning. Higher scores on symptom subscales reflected higher levels of symptoms.

Statistical analysis

We used X^2 statistics or the Fisher exact test for categorical variables and the *t* test or Mann-Whitney *U* test for continuous variables to compare patient and tumor characteristics (significance *p* value <.05). No specific power calculations were done for toxicity and HRQOL analysis. However, the sample size ensured sufficient power to detect clinically relevant differences. Toxicity and HRQOL were analyzed according to treatment received.

The prevalence of toxicity was calculated at each timepoint (using the maximum grade scored) and compared between the 2 treatment groups by the Fisher exact test.

Patients who completed baseline and at least 1 follow-up questionnaire were evaluable for HRQOL analysis. Missing data were handled as missing at random. As in previous analysis, a prespecified HRQOL analysis was done according to the EORTC Quality of Life Group guidelines.[5,15] A linear mixed model was used to obtain estimates for the EORTC QLQ-C30, CX24, and OV28 subscales at each of the timepoints, with patient as random effect and time (categorical), treatment, and their interaction as fixed effects. Single items were analyzed with generalized mixed models (binary) logistic regression with the same random and fixed effects as in the linear mixed model, combining scores of 1 to 2 ("not at all" and "a little") and 3 to 4 ("quite a bit" and "very much"). Additional linear mixed models were used within treatment arms with time, age, and their interaction as fixed effects. The difference in HRQOL between the groups over time was tested by a joint Wald test of all treatment-by-time interaction in the linear or logistic mixed model. Age-matched normative population means[16,17] were compared with both treatment groups using the *t* test. General population normative data of more than 1500 women across Europe and North America aged 60 to 69 years[16] were used for the EORTC QLQ-C30 scales, and general Dutch population normative data of 87 women aged 61 to 70 years were used for sexuality items.[17]

Guidelines on the interpretation of clinically relevant between-group differences in EORTC QLQ-C30 scores were applied (trivial, small, medium, or large differences per scale).[18] An additional post hoc analysis was performed to assess long-term (3-year and 5-year mean) changes from baseline at individual level. Between-group differences on scales not included in the guidelines and long-term changes were assessed according to Osoba et al.[19] Improvement and deterioration were defined respectively as a ≥10-point increase or decrease, and a stable score was defined as a <10-point change. Changes were compared between treatment groups using the Fisher exact test. In addition, Kendall's rank correlation was used post hoc to measure the ordinal association between different HRQOL items and scales. Finally, stepwise binary logistic regression with likelihood ratio test–based backward selection was performed to identify risk factors for developing tingling/numbness, including diabetes, cardiovascular disease, hypertension, age (≥70 years), type of surgery, performance status, and chemotherapy compliance.

To guard against false-positive results due to multiple testing, a 2-sided *p* value ≤.01 was considered statistically significant, and *p* values <.05 were reported as a trend. Statistical analyses were done with SPSS, version 25, and R, version 3.6.1.

Results

Study population and compliance

The PORTEC-3 trial accrued 660 eligible patients between 2006 and 2013; 333 patients received radiotherapy alone and 327 patients received chemoradiotherapy. At the time of analysis, median follow-up was 74.6 months (interquartile range, 60-86). Patient and treatment characteristics were well balanced between the groups (Table 1).

Baseline questionnaires and at least 1 follow-up questionnaire were received from 574 (87%) patients (292 in the chemoradiotherapy group and 282 in the radiotherapy-alone group). At 3 years, the completion rate was 89%, and at 5 years it was 63% (Appendix Table A1). Age distribution remained constant over time (data not shown). World Health Organization performance score differed between responders and nonresponders at baseline, with a score of ≥2 in 5 (1%) of the 574 responders versus 5 (6%) of the 86 non-responders (p = .005, Appendix Table A3). At baseline, 88% of the responders had completed all items of the EORTC QLQ-C30, 83% all items of the CX24 subscales, 95% all nonsexual items, and 91% all items of the OV28 subscale.

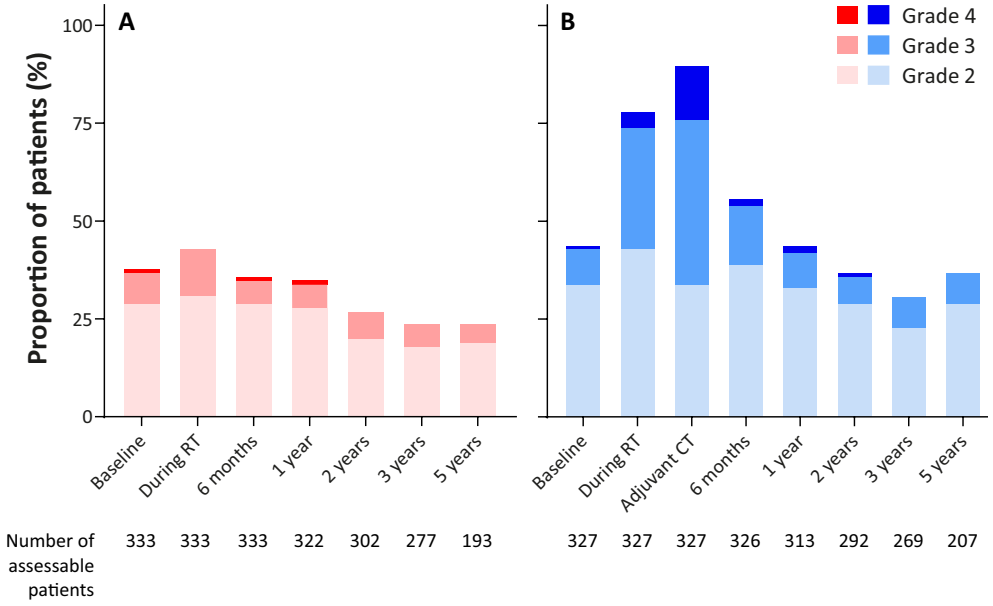

Figure 1. Incidence of the maximum physician-reported adverse event grades per patient for each timepoint at baseline, during treatment, at 6 months follow-up and at, 1, 2, 3 and 5 years follow-up after pelvic radiotherapy alone (A) and combined pelvic radiotherapy and chemotherapy (B).
CT = chemotherapy; RT = radiotherapy.

Table 1. Characteristics of as-treated population by treatment group.

	Chemoradiotherapy	**Radiotherapy alone**
	***n* = 327**	***n* = 333**
Age at randomization (y)		
Median	61.9 (55.9 - 68.1)	62.5 (56.5 - 68.0)
<60	127 (39%)	141 (42%)
60-69	142 (43%)	130 (39%)
≥70	58 (18%)	62 (19%)
WHO performance score		
0-1	320 (98%)	327 (98%)
2	5 (2%)	5 (2%)
Comorbidities		
Diabetes	45 (14%)	36 (11%)
Hypertension	115 (35%)	105 (32%)
Cardiovascular	29 (9%)	20 (6%)
FIGO 2009 stage		
Ia	39 (12%)	39 (12%)
Ib	58 (18%)	59 (18%)
II	79 (24%)	91 (27%)
III	151 (46%)	144 (43%)
Type of surgery		
TAH-BSO	94 (29%)	97 (29%)
TAH-BSO with LND or full staging	142 (44%)	134 (40%)
TLH-BSO	44 (13%)	44 (13%)
TLH-BSO with LND or full staging	47 (14%)	58 (17%)
Treatment completion		
RT completion	326 (100%)	328 (98%)
Brachytherapy boost	149 (46%)	160 (48%)
1 cycle cisplatin	325 (99%)	0
2 cycles cisplatin	304 (93%)	0
1 cycle carboplatin/paclitaxel	303 (93%)/303 (93%)	0
2 cycles carboplatin/paclitaxel	295 (90%)/295 (90%)	0
3 cycles carboplatin/paclitaxel	279 (85%)/266 (82%)	0
4 cycles carboplatin/paclitaxel	262 (80%)/235(72%)	0

Data are median (IQR) or *n* (%). FIGO = International Federation of Gynaecology and Obstetrics; TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy; LND = lymph node dissection; TLH = total laparoscopic hysterectomy; RT = radiotherapy.

Adverse events

AE reported over time are summarized in Table 2 and Figure 1. At baseline (after surgery), no significant between-group differences were found; grade ≥2 baseline AE were scored for 143 (44%) patients in the chemoradiotherapy group and 124 (37%) patients in the radiotherapy group. The most frequently scored AE was hypertension (27%). At 5 years, grade ≥2 AE were reported for 78 (38%) patients who had received chemoradiotherapy versus 46 (24%) patients who had received radiotherapy (p = .008); grade ≥2 sensory neuropathy persisted in 13 (6%) after chemoradiotherapy versus none after radiotherapy alone (p < .001). Other grade ≥2 AE did not significantly differ between groups at 5 years, including hypertension in 10% and urinary incontinence in 5% in both groups. Urinary urgency was reported in 9 (4%) versus 3 (2%) patients after chemoradiotherapy versus radiotherapy; any gastrointestinal toxicity in 17 (8%) versus 11 (6%), including diarrhea in 9 (4%) versus 7 (3%) and pain in 18 (9%) versus 9 (5%); and most often arthralgia in 11 (5%) versus 5 (3%). Grade 3 AE did not differ significantly between the groups at 5 years (5% vs 8%; p = .18), and only 1 new grade 4 AE was reported (ileus/obstruction requiring surgery 5 years after chemoradiotherapy).

HRQOL subscales

Results of the EORTC QLQ-C30 functioning and global health/quality of life (QOL) subscales and CX24 and OV28 subscales are summarized in Table 3. Up to 3 years, small clinically relevant differences were found for physical and role functioning (Figure 2A, 2B). At 3 years, mean scores were 79 versus 87 (p < .001) for physical functioning and 78 versus 88 (p < .001) for role functioning after chemoradiotherapy and radiotherapy, respectively; these scores were trivially different from the age-matched normative population. Long-term global health/QOL scores were not statistically or clinically different between the treatment groups. However, small to medium clinically relevant better scores were seen in the PORTEC-3 study population compared with the normative population (Figure 2C). Trends for worse long-term pain and fatigue symptom scores after chemoradiotherapy were seen, with the largest difference at 3 years (20.5 vs 14.1, p = .008; 26.0 vs 20.7, p = .015, respectively); these were small but clinically relevant differences. No long-term significant differences in social, cognitive, and emotional functioning were found between treatment groups or in comparison to the normative population (Appendix Figure A1, A2).

Among patients who had received chemoradiotherapy, age groups (<70 vs ≥70 years) differed in their change in scores over time for physical functioning (p < .001), role functioning (p = .011), global health/QOL (p < .001), pain (p = .004), and fatigue (p = .002); being more unfavorable in older patients. This also applies within the radiotherapy group for the physical and role functioning scores (p < .01), although not for global health/QOL (p = .42), pain (p = .33), and fatigue (p = .19). Data are displayed in Appendix Figure A3.

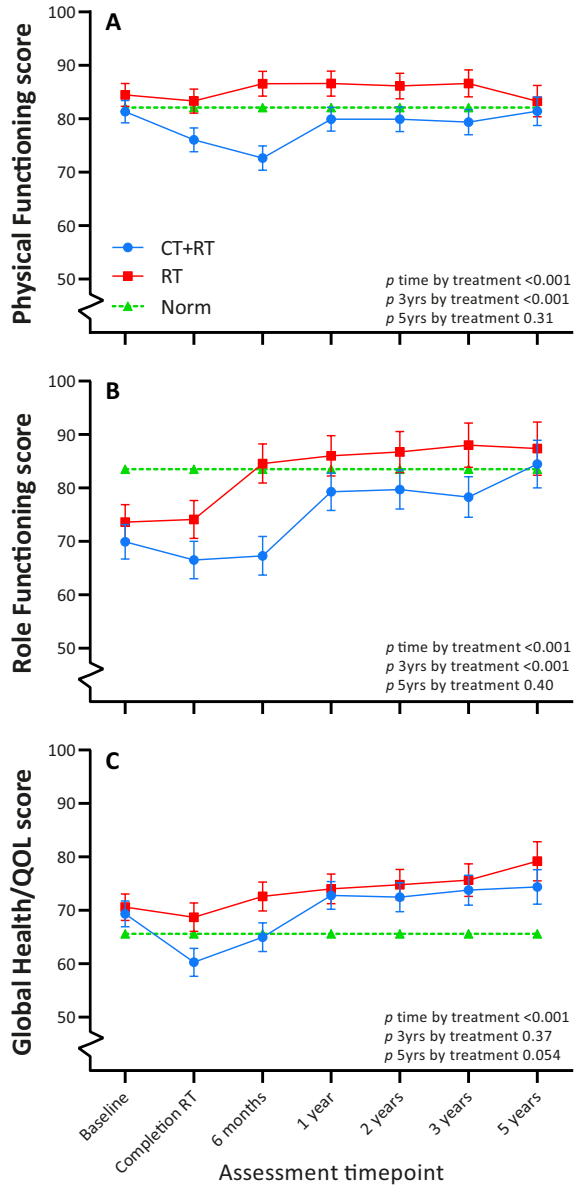

Figure 2. Patient functioning on subscales from EORTC QLQ-C30 for physical functioning (A), role functioning (B), global health status/quality of life (C).

A higher score indicates a higher level of functioning or activity. Error bars show 95% CI. EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; p time by treatment = difference between the two treatment groups over time; p 3yrs by treatment = difference between the two treatment groups at 3 years; p 5yrs by treatment = difference between the two treatment groups at 5 years; CT = chemotherapy; Norm = mean scores of age-match normative data based on women aged 60-69 years across 13 European countries, Canada and the United States;[16] RT = radiotherapy.

Table 2. Adverse events reported by physicians using Common Terminology Criteria for Adverse Events version 3.0 during treatment and at 3 and 5 years follow-up.

	Maximum grade per patient during treatment CTRT *n* = 327; RT *n* = 333						Maximum grade per patient at 3 years CTRT *n* = 269; RT *n* = 277						Maximum grade per patient at 5 years CTRT *n* = 207; RT *n* = 193					
	Grade 2			**Grade 3/4**			**Grade 2**			**Grade 3/4**			**Grade 2**			**Grade 3/4**		
	CTRT	**RT**	***p****	**CTRT**	**RT**	***p#***	**CTRT**	**RT**	***p****	**CTRT**	**RT**	***p#***	**CTRT**	**RT**	***p****	**CTRT**	**RT**	***p#***
	***n* (%)**	***n* (%)**		***n* (%)**	***n* (%)**		***n* (%)**	***n* (%)**		***n* (%)**	***n* (%)**		***n* (%)**	***n* (%)**		***n* (%)**	***n* (%)**	
Any	110 (34)	103 (31)	<0.01	198 (61)	41 (12)	<0.01	63 (23)	49 (18)	0.04	21(8)	16 (6)	0.40	60 (29)	37 (19)	<0.01	18 (9)	9 (5)	0.18
Any grade 3	na	na		148 (45)	41 (12)		na	na		20 (7)	16 (6)		na	na		17 (8)	9 (5)	
Any grade 4	na	na		50 (15)	0 (0)		na	na		1 (0)	0 (0)		na	na		1 (0)	0 (0)	
Auditory/hearing	14 (4)	3 (1)	<0.01	1 (0)	1 (0)	1.00	1 (0)	1 (0)	1.00	1 (0)	1 (0)	1.00	4 (2)	1 (1)	0.29	2 (1)	1 (1)	1.00
Hypertension	19 (6)	12 (4)	0.10	6 (2)	3 (1)	0.34	15 (6)	17 (6)	0.75	5 (2)	6 (2)	1.00	16 (8)	17 (9)	0.63	4 (2)	5 (3)	0.74
Lymphatics (edema)	7 (2)	4 (1)	0.17	2 (1)	0 (0)	0.25	3 (1)	1 (0)	0.12	2 (1)	0 (0)	0.24	5 (2)	2 (1)	0.45	0 (0)	0 (0)	1.00
Gastrointestinal - any	145 (44)	79 (24)	<0.01	47 (14)	18 (5)	<0.01	11 (4)	17 (6)	0.46	2 (1)	1 (0)	0.62	15 (7)	10 (5)	0.43	2 (1)	1 (1)	1.00
Diarrhea	103 (31)	68 (20)	<0.01	35 (11)	14 (4)	<0.01	4 (1)	8 (3)	0.42	1 (0)	1 (0)	1.00	7 (3)	7 (4)	0.80	2 (1)	0 (0)	0.50
Ileus/obstruction	3 (1)	5 (2)	0.77	2 (1)	2 (1)	1.00	0 (0)	0 (0)	0.49	1 (0)	0 (0)	0.49	2 (1)	1 (1)	0.22	3 (1)	0 (0)	0.25
Hematological - any	100 (31)	19 (6)	<0.01	149 (46)	18 (5)	<0.01	3 (1)	3 (1)	1.00	1 (0)	2 (1)	1.00	5 (2)	5 (3)	1.00	0 (0)	0 (0)	1.00
Lymphocytes	48 (15)	16 (5)	<0.01	109 (33)	17 (5)	<0.01	1 (0)	0 (0)	0.49	0 (0)	0 (0)	1.00	3 (1)	4 (2)	0.72	0 (0)	0 (0)	1.00
Neuropathy - any	82 (25)	1 (0)	<0.01	23 (7)	0 (0)	<0.01	18 (7)	2 (1)	<0.01	2 (1)	0 (0)	0.24	13 (6)	0 (0)	<0.01	1 (0)	0 (0)	1.00
Neuropathy - motor	13 (4)	1 (0)	<0.01	4 (1)	0 (0)	0.06	3 (1)	2 (1)	0.44	1 (0)	0 (0)	0.49	1 (0)	0 (0)	0.50	1 (0)	0 (0)	1.00
Neuropathy - sensory	79 (24)	0 (0)	<0.01	22 (7)	0 (0)	<0.01	18 (7)	1 (0)	<0.01	2 (1)	0 (0)	0.24	12 (6)	0 (0)	<0.01	1 (0)	0 (0)	1.00
Pain - any	101 (31)	23 (7)	<0.01	31 (9)	4 (1)	<0.01	17 (6)	15 (5)	0.30	4 (1)	0 (0)	0.06	15 (7)	6 (3)	0.12	3 (1)	3 (2)	1.00
Arthralgia	52 (16)	2 (1)	<0.01	10 (3)	0 (0)	<0.01	2 (1)	5 (2)	0.73	1 (0)	0 (0)	0.49	9 (4)	4 (2)	0.20	2 (1)	1 (1)	1.00
Muscle pain	52 (16)	1 (0)	<0.01	9 (3)	0 (0)	<0.01	3 (1)	0 (0)	0.12	0 (0)	0 (0)	1.00	1 (0)	1 (1)	0.61	0 (0)	1 (1)	0.48
Back/pelvic/limbs	10 (3)	4 (1)	<0.01	11 (3)	0 (0)	<0.01	4 (1)	3 (1)	0.50	1 (0)	0 (0)	0.49	0 (0)	2 (1)	0.11	0 (0)	1 (1)	0.48
Abdomen/cramps	14 (4)	9 (3)	0.28	4 (1)	4 (1)	1.00	5 (2)	1 (0)	0.07	1 (0)	0 (0)	0.49	2 (1)	0 (0)	0.12	2 (1)	0 (0)	0.50
Musculoskeletal (other)	2 (1)	2 (1)	0.50	2 (1)	0 (0)	0.50	1 (0)	0 (0)	0.24	1 (0)	0 (0)	0.49	0 (0)	1 (1)	1.00	0 (0)	0 (0)	1.00
Pulmonary - dyspnea	14 (4)	2 (1)	0.25	5 (2)	0 (0)	0.03	1 (0)	0 (0)	1.00	0 (0)	1 (0)	1.00	2 (1)	0 (0)	0.50	0 (0)	0 (0)	1.00
Genitourinary																		
Incontinence	12 (4)	5 (2)	0.06	1 (0)	0 (0)	0.50	8 (3)	3 (1)	0.09	1 (0)	0 (0)	0.49	8 (4)	9 (5)	1.00	0 (0)	0 (0)	1.00
Obstruction	0 (0)	1 (0)	1.00	0 (0)	0 (0)	1.00	0 (0)	0 (0)	0.49	0 (0)	1 (0)	0.49	0 (0)	0 (0)	1.00	0 (0)	0 (0)	1.00
Urinary urgency	24 (7)	10 (3)	0.01	2 (1)	2 (1)	1.00	7 (3)	5 (2)	0.57	0 (0)	0 (0)	1.00	9 (4)	3 (2)	0.14	0 (0)	0 (0)	1.00
Constitutional																		
Fatigue	69 (21)	7 (2)	<0.01	10 (3)	0 (0)	<0.01	1 (0)	0 (0)	0.49	0 (0)	0 (0)	1.00	0 (0)	3 (2)	0.11	0 (0)	0 (0)	1.00
Other	31 (9)	2 (1)	<0.01	3 (1)	0 (0)	0.12	1 (0)	0 (0)	0.24	1 (0)	0 (0)	0.49	2 (1)	0 (0)	0.25	1 (0)	0 (0)	1.00
Other toxicity	0 (0)	0 (0)	1.00	0 (0)	0 (0)	1.00	0 (0)	1 (0)	1.00	1 (0)	0 (0)	0.49	2 (1)	2 (1)	0.69	2 (1)	0 (0)	0.50

Adverse events were calculated at each timepoint. Per adverse event, the maximum grade per patient was calculated (worst ever by patient). For grade 2, 3, and 4 adverse events, *p* values less than or equal to 0.01 were deemed significant. *p** = significant level < 0.01 for grade ≥2. *p#* = significant level <0.01 for grade 3 and 4.

CTCAE v3.0 = Common Terminology Criteria for Adverse Events version 3.0; CTRT = combined chemotherapy and radiotherapy; RT = radiotherapy.

Table 3. Patient reported health-related quality of life using the EORTC QLQ-C30 and subscales of CX-24 and OV-28.

		Questionnaire time points						*p*-value					Norm	
				Months										
		Baseline	After RT	6	12	36	60	Time	Tx	Time by Tx	at 3yr	at 5yr	60-69 yr	CS
EORTC QLQ C30 functioning scales														
Physical functioning	CTRT	81.3	76.0	72.6	79.9	79.4	81.4	**<0.001**	**<0.001**	**<0.001**	**<0.001***	0.31	82.1	T
	RT	84.5	83.3	86.5	86.6	86.6	83.5							T
Role functioning	CTRT	69.9	66.5	67.3	79.3	78.3	84.5	**<0.001**	**<0.001**	**<0.001**	**0.0007***	0.40	83.5	T
	RT	73.6	74.1	84.6	86.0	88.0	87.4							T
Emotional functioning	CTRT	74.4	76.9	77.0	80.7	81.6	84.6	**<0.001**	0.14	**<0.001**	0.33	0.80	77.8	**S**
	RT	77.4	81.5	80.8	82.7	83.5	84.0							**S**
Cognitive functioning	CTRT	86.9	81.4	79.4	83.8	83.4	86.8	**<0.001**	**0.0022**	0.035	0.18	0.66	87.9	T
	RT	87.9	85.8	86.9	87.3	86.4	87.8							T
Social functioning	CTRT	77.7	73.5	74.0	84.2	85.4	90.2	**<0.001**	**<0.001**	**<0.001**	0.43	0.72	88.1	T
	RT	80.1	78.7	88.1	89.9	87.2	91.2							T
Global health status/ Quality of Life	CTRT	69.3	60.3	65.0	72.8	73.8	74.4	**<0.001**	**<0.001**	**<0.001**	0.37	0.054	65.6	**S**
	RT	70.6	68.7	72.6	74.0	75.7	79.2							**M**
QLQ C30 Symptoms scales														
Fatigue	CTRT	29.0	42.4	38.4	28.2	26.0	23.3	**<0.001**	**<0.001**	**<0.001**	0.015	0.058	26.6	T
	RT	26.6	34.4	23.8	22.8	20.7	18.4							**S**
Nausea and vomiting	CTRT	3.7	14.1	9.1	5.1	3.7	4.2	**<0.001**	**<0.001**	**<0.001**	0.67	0.81	3.7	T
	RT	4.0	10.2	5.7	6.1	4.3	3.8							T
Pain	CTRT	18.4	21.6	23.5	21.1	20.5	16.2	0.008	0.04	0.09	**0.0075***	0.34	25.4	**S**
	RT	17.1	19.1	16.9	15.6	14.1	13.5							**S**
CX 24 subscales/items														
Symptom experience‡	CTRT	9.7	16.2	12.2	11.8	12.3	12.1	**<0.001**	0.6	0.0047	0.56	0.59		
	RT	9.5	16.9	11.8	12.5	11.7	11.5							
Body image‡	CTRT	12.0	17.2	25.3	16.9	16.4	13.7	**<0.001**	**<0.001**	**<0.001**	**0.0053***	0.25		
	RT	10.0	13.1	13.0	11.9	10.6	11							
Sexual functioning‡	CTRT	14.3	21.3	19.0	20.4	23.4	25.3	0.059	0.53	**<0.001**	0.83	0.92		
	RT	11.5	23.2	22.5	24.3	26.0	26.2							
OV 28 subscales														
Chemotherapy‡	CTRT	6.2	18.9	31.7	14.9	14.6	14.9	**<0.001**	**<0.001**	**<0.001**	**0.0083**	0.061		
	RT	7.8	11.0	12.1	11.5	10.8	11.7							
Peripheral neuropathy‡	CTRT	5.5	14.8	47.1	32.4	28.8	23.5	**<0.001**	**<0.001**	**<0.001**	**<0.001†**	**0.0032***		
	RT	5.5	8.7	12.5	11.3	13.6	16.3							

All subscales responses were converted to 0 to 100 scales (according to the EORTC guidelines). Higher scores for functioning items and global quality of life scale represent a better level of functioning. For the symptom scales, a higher score reflects a higher level of symptoms.

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire C30; CTRT = combined chemotherapy and radiotherapy; RT = radiotherapy; Norm = age-matched normative population.[16] CX = cervix; OV = ovarian; HRQOL = health-related quality of life; Tx = treatment; *p* Time = changes of quality-of-life scores over time; *p* Tx = difference between the two treatment groups; *p* Time by Tx = difference between the two treatment groups over time; *p* Tx at 3yr = difference between the two treatment groups at 3 years; *p* Tx at 5yr = difference between the two treatment groups at 5 years; CS = clinical significance at 5 years; T = trivial difference; S = small difference; M = medium difference. Bold values denote statistical significance at the $p<0.01$ level; Bold values in the 'Norm'-column denote statistically significant and clinically relevant small/medium differences compared to 5-years study-patients' score.

*Clinically relevant small difference.

†Clinically relevant medium difference.

‡Items included in the subscale are specified in supplementary Table A2.

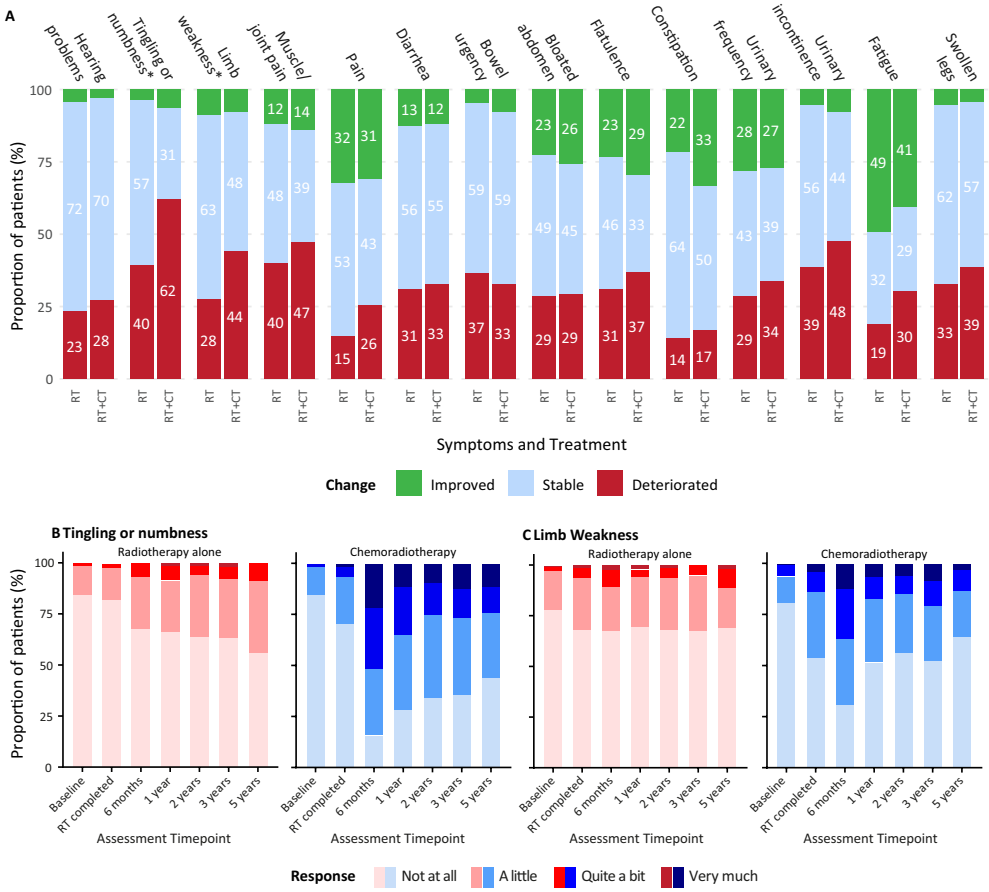

Figure 3. Clinically relevant long-term changes compared to baseline in patient reported symptoms on EORTC QLQ-C30, CX24 and OV28 on individual patient level (A) and patient responses on single-items with significant change: tingling or numbness (B) and limb weakness (C).
Long-term change is defined as the mean of 3 and 5 year scores compared to baseline score on individual level. CT = chemotherapy; RT = radiotherapy.

Symptom items

A complete overview of the proportion of patients reporting significant ("quite a bit" or "very much") symptoms is shown in Appendix Table A2. Patients treated with chemoradiotherapy reported more significant tingling or numbness throughout the 5-year follow-up period compared with patients who received radiotherapy alone. At 5 years, 32 (24%) patients treated with chemoradiotherapy reported significant tingling/numbness, in contrast to 9 (9%) treated with radiotherapy ($p = .002$). Likewise, 129 (62%) versus 66 (40%) patients had deteriorated in tingling/numbness compared with baseline ($p < .001$, Figure 3 and Appendix Figure A5A); no difference between patients with or without diabetes was found among patients treated with chemotherapy (Appendix

Figure A4C and A5B). A trend toward worse tingling/numbness in patients aged ≥70 years was found over time after chemoradiotherapy ($p = .016$) but not after radiotherapy ($p = .35$, Figure A4B). None of variables entered in the multivariate logistic regression model were statistically significant risk factors for tingling/numbness (data not shown).

Chemoradiotherapy patients reported more significant limb weakness up to 3 years (21% after chemoradiotherapy vs 5% after radiotherapy at 3 years, $p < .001$), with deterioration at 3 and 5 years compared with baseline in 92 (44%) patients after chemoradiotherapy versus 46 (28%) after radiotherapy ($p = .003$, Figure 3). No between-group differences in long-term change of gastrointestinal and bladder symptoms were seen (Figure 3).

Sexual activity did not differ between the 2 treatment groups at 3 and 5 years (Appendix Table A2). Sexual activity was reported by 69 (34%) patients (both treatment groups combined) at 5 years. Among those sexually active, 14 (19%) patients reported significant pain during sex; 20 (27%) reported significant vaginal dryness, and 58 (80%) reported sex to be enjoyable. Mean sexual activity scores were lower than those of the age-matched normative population, with a clinically relevant moderate difference ($p < .001$; Appendix Figure A6).

Correlation

The strongest between-functioning score correlations were found for physical and role functioning ($\tau = 0.66$), for social and role functioning ($\tau = 0.61$), for global health/QOL and role functioning ($\tau = 0.58$), and for global health/QOL and physical functioning ($\tau = 0.53$). The strengths of the negative correlations between symptoms and functioning varied from -0.12 to -0.64, with the strongest correlation for fatigue, closely followed by pain, limb weakness, muscle/joint pain, and lower back pain. The correlation between these symptoms also was relatively strong ($\tau = 0.39$-0.55). Finally, there were significant negative correlations for tingling/numbness and physical functioning ($\tau = -0.32$), role functioning ($\tau = -0.30$), global health/QOL ($\tau = -0.26$), and the other functioning scales ($\tau = -0.22$ to -0.25). A comprehensive correlation matrix is displayed in Appendix Figure A7.

Discussion

This long-term analysis of toxicity and HRQOL in the PORTEC-3 trial shows that combined adjuvant chemoradiotherapy for high risk endometrial cancer may have a long-lasting clinically relevant negative impact on quality of life, with a small long-term deterioration in physical and role functioning for the first 3 years after treatment compared with radiotherapy alone. Patients treated with chemoradiotherapy reported significantly more prominent limb weakness until 3 years and persistent tingling or numbness in hands

or feet throughout the 5-year follow-up period. In addition, more grade ≥2 toxicity was reported at 5 years (38% vs 24%). Despite these persistent symptoms, the treatment groups had similar long-term global health/QOL scores that were in fact better than those of the age-matched normative population. This is the first comprehensive documentation of long-term patient-reported symptoms and HRQOL after chemoradiotherapy in endometrial cancer, with the strength of comparison to pelvic radiotherapy alone and to an age-matched normative population, exclusion of biases due to the randomization, and complete follow-up. These data are essential for patient counseling and shared decision making on adjuvant therapy in high risk endometrial cancer.

The present study found remaining grade ≥2 sensory neuropathy in 6% after chemoradiotherapy, with HRQOL showing "quite a bit" or "very much" tingling/numbness being reported by 24% at 5 years. The recovery was largest in the first months after chemotherapy and improved until 2 years to a stable level. In comparison, less than 10% of the patients reported long-term significant tingling/numbness after radiotherapy alone (no reported grade ≥2 AE), which seemed most likely due to diabetic and idiopathic peripheral neuropathy in this elderly population.[20] Because limited agreement between patient and physician scoring of toxicities has been reported,[21] physicians were required to report grade ≥2 AE to focus on more severe toxicities, whereas patient-reported outcomes were used for mild toxicities. Reported data on long-term toxicity and HRQOL of women treated with carboplatin and paclitaxel chemotherapy, although limited, are available from trials of first-line therapy in ovarian cancer. This comparison is relevant because patients with ovarian cancer are of similar age and had previous pelvic surgery without radiotherapy. Similar levels of patient-reported persistent tingling/numbness with a comparable pattern of recovery after chemotherapy were seen in studies of ovarian cancer survivors.[6,9] The randomized GOG-249 trial, in which 3 cycles of carboplatin and paclitaxel with vaginal brachytherapy were compared with pelvic radiotherapy alone in women with high-intermediate and high risk stage I-II endometrial cancer, also showed significantly higher chemotherapy-induced peripheral neuropathy (CIPN) rates in the chemotherapy arm (sensory neuropathy grade ≥2 in 10% at 2 years), even while using only 3 cycles. Detailed analysis on HRQOL in the GOG-249 trial is pending.[22]

Another important persistent symptom after chemoradiotherapy was limb weakness, which might be interpreted as a result of motor CIPN. However, limb weakness was found to be more strongly correlated to fatigue and muscle/joint pain than to tingling/numbness; this finding supports previous studies suggesting that limb weakness is more a general symptom, associated with fatigue and reduced physical functioning.[6,23]

The correlation coefficient ($\tau = 0.32$) found between tingling/numbness and physical functioning means that a patient with a higher tingling/numbness score had a 66% chance of also having a worse functioning score compared with another patient. This suggests that tingling/numbness is associated with impaired functioning, although correlations for other symptoms (limb weakness, fatigue, and pain) and functioning and global health/QOL were stronger. Most nonlongitudinal studies investigating the correlation between sensory neuropathy and functioning in various cancer types found a negative correlation.[6, 7, 8,10,11] Bonhof et al.[9] found significant functioning differences between patients with and without limb weakness, but not for tingling/numbness at 2 years, possibly due to the small sample size. In general, it seems that functioning is negatively influenced by several symptoms, including tingling/numbness, limb weakness, fatigue, and pain.

In this long-term analysis, it seemed that chemoradiotherapy patients further improved between 3 and 5 years of follow-up in physical and role functioning and limb weakness. It is possible that the relatively high attrition rate (around 30%) between 3 and 5 years might introduce some response bias. A small part of the attrition at this timepoint is explained by death or recurrence; however, other reasons for missing questionnaires were not collected. Notably, chemoradiotherapy patients who responded only at 3 years reported significantly more significant muscle/joint pain, symptoms that were strongly correlated to physical and role functioning, than patients who responded both at 3 and 5 years. Another explanation could be that patients adjust their lives to bothersome but manageable symptoms, which is also suggested by the improvement in long-term global health/QOL scores in both treatment groups. Moreover, possible bias due to the Hawthorne effect should be taken into consideration when comparing normative to trial population data; patients participating in trials may report better QOL than normative populations.

One limitation of the study is that toxicity, even though scored by a physician according to the CTCAE classification, remains a subjective measurement. At baseline, grade ≥2 hypertension was scored in 27% of the patients, corresponding to the on-study form reporting 33% patients having hypertension with medication. At subsequent timepoints, hypertension was only scored in about 10% of the patients. This implies that during and after therapy, oncologists focus on treatment-related AE, resulting in underreporting of unrelated conditions primarily managed by family doctors such as hypertension, which is especially important in interpreting changes from baseline. Because the bias occurred in both groups, it has negligible impact on long-term between-group comparison.

The contemporary challenge is to avoid significant symptoms caused by chemotherapy by developing preventive strategies and intervention measures. Unfortunately, there is currently no effective treatment or prevention strategy against CIPN.[24] This study was unable to identify risk factors for persistent CIPN, which is unfortunate because data on risk factors for developing CIPN are inconsistent.[25] Limitations to drawing any conclusion include the selected study population based on inclusion criteria and insufficient power related to small groups. Nevertheless, patients aged 70 years or older scored generally worse over time than younger patients, even though this was a selected population of relatively fit women. This age-based difference, particularly for global health/QOL and symptoms of pain, fatigue and tingling/numbness is more pronounced after chemoradiotherapy compared with radiotherapy. Older patients seemed to have a relatively greater failure-free survival benefit from chemotherapy.[12] Therefore, specific patient counseling is recommended for older patients.

No between-group differences were found for gastrointestinal and bladder symptoms, largely explained by the use of pelvic radiotherapy in both arms. The reported gastrointestinal symptoms (eg, urgency and diarrhea in about 10% of the patients) and bladder symptoms (urgency ±25%, incontinence ±10%) are consistent with the rates found after pelvic radiotherapy in the PORTEC-2 trial.[26] The incidence of gastrointestinal symptoms is expected to remain more or less stable, and urinary symptoms are expected to slightly deteriorate in the following years owing to the combined effects of radiotherapy and aging on the pelvic floor and bladder.[3,4]

The overall survival benefit of chemoradiotherapy compared with radiotherapy alone in high risk endometrial cancer was 5% at 5 years for the complete trial population, with the greatest benefit of ≥10% observed in women with serous cancers and those with stage III disease.[2] Molecular classification can be used to more effectively identify subgroups that benefit most from chemotherapy.[27] For example, molecular classification in clinical diagnostics might lead to the specific recommendation of chemoradiotherapy in those with *TP53*-mutated tumors, and chemotherapy might be omitted in *POLE*mut and mismatch repair deficient tumors. Women with high risk mismatch repair deficient tumors might be better treated with adjuvant immunotherapy, with a different but generally more favorable toxicity profile than carboplatin-paclitaxel chemotherapy.

The trade-off between the benefit and the short- and long-term toxicities of chemotherapy should be discussed as part of shared decision making. To better guide shared decision making, it is important to know what patients consider important in this trade-off. In a patient preference study done by the ANZGOG group among their PORTEC-3 participants, more than 50% of women reported a 5% survival improvement as being sufficient to make chemotherapy worthwhile.[28] No study to date has examined which factors are prioritized by patients and clinicians in this decision-making process and what survival improvement would be sufficient to make chemotherapy worthwhile based on the actual symptoms and HRQOL impairment in the PORTEC-3 trial. This is currently being investigated in a Dutch trade-off study in patients with high risk endometrial cancer and their health care professionals.

Conclusions

This study shows a long-lasting, clinically relevant, negative impact of combined chemotherapy and radiotherapy on toxicity and qulaity of life compared with radiotherapy alone, with persistent peripheral sensory neuropathy at 5 years in 24% of patients and small but clinically relevant differences in physical and role functioning until 3 years. These results provide essential information to be used for patient counseling and shared decision making.

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APPENDIX A

Table A1. Questionnaire response during follow up

	Questionnaire time points							
			Months					
	Baseline	After RT	6	12	18	24	36	60
Responders CT+RT (*n*)	292	236	223	238	217	214	194	132
Responders RT (*n*)	282	231	214	201	189	185	159	103
Responders Total (*n*)	574	467	437	439	406	399	353	235
Patients on assessment (*n*)	660	552	528	487	458	417	395	374
Available data rate[a]	87%	71%	66%	67%	62%	61%	53%	36%
Completion rate[b]	87%	85%	83%	90%	89%	96%	89%	63%

CT = chemotherapy, RT = radiotherapy.

[a] Calculation of the 'fixed' denominator rate: Numerator as 'number of patients on PRO assessment submitting the PRO assessment at the designated time point' and denominator as 'number of patients in the PRO study population (all study patients, *n* = 660)'.

[b] Calculation of the 'variable' denominator rate: Numerator as 'number of patients on PRO assessment submitting the PRO assessment at the designated time point' and denominator as 'Number of patients on PRO assessment at the designated time point (Patients on assessment = total study population with completed baseline questionnaire excluding deceased patients or patients with recurrent disease)'. Used terms are defined according to SISAQOL recommendations.[1]

Table A2. Complete overview of percentages of patients reporting 'quite a bit' or 'very much' HRQOL symptoms using the EORTC QLQ-C30 and subscales of CX-24 and OV-28.

		Questionnaire time points										
		Baseline	After RT	6m	12m	24m	36m	60m	*p*-value Time	Tx	Time by Tx	Tx at 3 years	Tx at 5 years
QLQ-C30 symptoms													
Dyspnoea	CTRT	5.4	11.0	15.4	7.5	8.0	11.2	8.5	0.0040	0.030	0.16	0.14	0.83
	RT	2.8	5.2	5.1	5.0	4.1	6.3	5.8					
Insomnia	CTRT	24.5	25.2	25.1	17.8	18.8	23.5	19.8	0.34	0.50	0.75	0.11	0.10
	RT	18.8	19.0	18.6	14.6	12.4	14.4	10.7					
Appetite loss	CTRT	6.4	23.6	11.2	2.5	3.3	3.6	5.3	<0.001	0.038	0.15	0.8	0.10
	RT	4.5	15.7	4.7	3.4	3.6	3.8	1.0					
Constipation	CTRT	11.5	4.6	8.2	3.7	4.7	7.3	5.3	0.0047	0.059	0.12	0.14	0.42
	RT	7.0	1.3	1.9	4.0	3.1	2.5	2.9					
Diarrhoea	CTRT	5.1	36.1	12.7	10.4	9.9	11.8	14.5	<0.001	0.96	0.024	0.63	0.23
	RT	3.8	36.8	12.6	11.3	10.9	10.1	7.8					
Financial difficulties	CTRT	12.2	11.9	15.9	8.7	6.5	6.6	2.3	<0.001	0.012	0.0083	0.16	0.044
	RT	7.7	7.5	7.0	3.0	4.2	3.1	4.9					
CX24													
Bowel symptoms													
1. Abdominal cramps	CTRT	6.8	17.8	9.9	9.2	10.8	9.7	6.1	<0.001	0.79	0.86	0.2	0.66
	RT	6.0	15.5	9.0	10.4	7.3	6.3	7.8					
1. Difficulty controlling bowels	CTRT	3.1	20.3	9.9	9.1	7.5	9.7	9.2	<0.001	0.61	0.0012	0.43	0.87
	RT	1.4	20.3	10.9	10.4	12.2	8.2	8.7					
1. Blood in stools	CTRT	0.7	0.8	0.9	0.0	2.4	0.0	0.8	0.70	0.96	1.00	0.90	0.92
	RT	0.4	0.4	0.9	0.5	0.5	0.6	0.0					
Urinary symptoms													
1. Urninary frequency	CTRT	23.3	38.6	22.1	23.0	17.5	23.5	27.3	<0.001	0.89	0.83	0.93	0.85
	RT	21.8	36.6	16.9	22.8	20.4	20.9	22.5					
1. Dysuria	CTRT	5.8	17.3	1.4	2.5	1.9	3.1	2.3	<0.001	0.67	0.31	0.51	0.76
	RT	4.2	14.7	3.8	3.0	1.6	1.3	1.0					
1. Urinary leakage	CTRT	2.7	6.8	8.6	7.9	9.3	16.4	10.6	<0.001	0.034	<0.001	0.026	0.94
	RT	4.2	4.3	4.7	8.9	9.9	8.9	10.7					
1. Difficulty emptying the bladder	CTRT	4.4	5.1	2.3	1.7	2.8	5.7	3.8	0.12	0.39	0.40	0.12	0.77
	RT	3.2	4.8	2.8	3.5	3.7	1.9	3.9					
Other													
Swollen legs	CTRT	2.4	5.5	18.0	16.3	12.7	7.6	15.3	<0.001	0.10	<0.001	0.018	0.47
	RT	2.5	3.0	11.3	10.9	14.1	16.9	13.6					
1. Lower back pain	CTRT	10.5	10.2	16.6	18.8	18.7	22.2	22.3	<0.001	0.86	0.0079	0.40	0.13
	RT	9.2	7.8	16.0	14.3	16.6	14.6	12.7					

Table A2. Complete overview of percentages of patients reporting 'quite a bit' or 'very much' HRQOL symptoms using the EORTC QLQ-C30 and subscales of CX-24 and OV-28 *(continued)*.

		Questionnaire time points				*p*-value							
		Baseline	After RT	6m	12m	24m	36m	60m	Time	Tx	Time by Tx	Tx at 3 years	Tx at 5 years
Tingling/numbness	CTRT	1.7	6.4	51.8	34.9	25.2	26.8	24.2	<0.001	<0.001	<0.001	<0.001	0.0026
	RT	1.4	2.6	6.7	8.5	5.8	7.6	8.8					
1. Irritation/soreness vagina/vulva	CTRT	2.7	8.1	5.0	3.8	1.4	2.1	4.6	0.001	0.33	0.14	0.18	0.62
	RT	1.4	11.7	3.8	5.5	3.1	3.8	4.9					
1. Vaginal discharge	CTRT	2.7	2.6	2.3	2.1	0.9	2.5	1.5	0.98	0.91	0.89	0.57	0.81
	RT	1.8	4.3	0.5	1.5	0.5	1.5	1.9					
1. Vaginal bleeding abnormal	CTRT	0.7	1.3	1.3	1.3	0.5	0.0	0.8	0.95	0.98	0.99	0.88	0.86
	RT	1.0	0.4	0.9	0.5	0.5	0.6	0.0					
Hot flushes and/or sweats	CTRT	16.9	14.8	20.4	18.8	17.2	20.9	14.4	0.19	0.37	0.27	0.94	0.97
	RT	12.7	15.6	24.5	22.8	22.0	22.0	15.5					
Body Image													
2. Feeling of physically less attractive	CTRT	5.5	14.4	26.1	11.1	8.9	10.8	8.3	<0.001	<0.001	0.34	0.046	0.17
	RT	3.4	6.9	7.5	4.4	4.2	5.1	3.9					
2. Feeling less feminine	CTRT	5.1	9.3	16.1	10.8	8.4	10.3	5.3	<0.001	0.044	0.71	0.014	0.38
	RT	3.5	7.0	6.6	5.4	4.7	4.5	3.9					
2. Dissatisfied with body	CTRT	5.8	10.5	18.1	13.6	11.6	14.9	15.2	<0.001	0.37	0.0041	0.39	0.09
	RT	3.9	8.8	9.4	9.4	6.3	10.1	6.9					
Sexual functioning													
Worries about sex	CTRT	13.8	21.5	20.1	17.1	12.8	14.6	11.1	0.049	0.57	0.64	0.15	0.41
	RT	14.3	20.2	15.3	13.6	14.0	9.5	17.2					
Sexual activity†	CTRT	11.9	18.6	29.2	33.9	33.5	33.5	30.8	<0.001	0.14	<0.001	0.48	0.10
	RT	9.7	21.5	41.9	42.2	36.0	37.3	37.0					
3. Vaginal dryness*	CTRT	10.0	18.8	24.6	29.9	22.4	28.1	21.6	0.22	0.63	0.029	0.5	0.43
	RT	4.3	23.6	21.1	24.2	31.3	28.8	31.6					
3. Shortness of vagina*	CTRT	4.2	8.5	10.1	15.8	21.5	22.4	13.2	0.24	0.96	0.10	0.62	0.98
	RT	2.2	10.9	14.1	18.9	22.7	15.5	21.6					
3. Tightness of vagina*	CTRT	6.4	27.6	19.4	17.1	15.2	29.3	13.5	0.038	0.071	0.0037	0.42	0.46
	RT	4.3	13.0	21.3	21.1	25.0	20.7	24.3					
3. Pain during sexual intercourse*	CTRT	0.0	25.0	16.2	10.7	11.9	19.6	8.1	0.15	0.22	0.023	0.92	0.13
	RT	4.7	18.3	17.0	20.9	23.5	20.0	29.7					
Sexual activity enjoyable?*†	CTRT	50.0	57.5	75.0	77.8	81.8	80.4	83.8	0.056	0.49	0.30	0.46	0.77
	RT	61.0	74.5	75.0	77.8	76.1	83.1	75.0					
OV28													
Bloated feeling abdomen/stomach	CTRT	13.0	1.7	19.5	11.3	11.3	11.9	13.0	0.054	0.59	0.56	0.69	0.42
	RT	11.2	14.4	14.4	15.3	10.5	12.1	10.0					

Table A2. Complete overview of percentages of patients reporting 'quite a bit' or 'very much' HRQOL symptoms using the EORTC QLQ-C30 and subscales of CX-24 and OV-28 *(continued)*.

		Questionnaire time points				*p*-value							
		Baseline	After RT	6m	12m	24m	36m	60m	Time	Tx	Time by Tx	Tx at 3 years	Tx at 5 years
Passing wind/gas/flatulence	CTRT	17.6	20.3	24.0	21.3	22.4	21.4	22.3	0.7	0.52	0.43	0.29	0.25
	RT	11.8	18.7	19.6	21.3	17.6	15.9	14.9					
4. Loss of any hair	CTRT	1.4	11.1	45.2	4.6	0.5	2.1	3.9	<0.001	<0.001	<0.001	0.24	0.41
	RT	0.4	3.1	4.3	3.0	2.1	0.6	2.0					
4. Upset by loss of hair**	CTRT	3.3	25.0	41.9	29.3	11.1	16.2	20.0	<0.001	0.013	0.26	0.28	0.11
	RT	5.3	3.6	15.9	9.3	7.3	6.1	4.8					
4. Different taste of food and drink	CTRT	3.5	26.2	22.3	3.9	1.9	4.2	4.0	<0.001	<0.001	0.46	0.11	0.86
	RT	0.7	9.4	4.3	1.5	1.6	1.9	0.0					
5. Tingling hand/feet	CTRT	1.1	7.2	49.3	26.8	23.4	25.4	21.4	<0.001	<0.001	<0.001	<0.001	0.018
	RT	1.4	2.2	5.8	4.1	5.4	4.5	10.2					
5. Numbness fingers/toes	CTRT	1.4	5.5	50.0	29.6	25.5	24.4	19.7	<0.001	<0.001	<0.001	<0.001	0.029
	RT	0.4	2.7	4.9	2.6	4.3	8.3	8.3					
5. Weakness arms/legs	CTRT	6.3	14.2	36.8	17.5	15.1	20.7	13.3	<0.001	<0.001	<0.001	<0.001	0.52
	RT	2.9	6.3	11.0	5.7	6.3	5.1	11.3					
4. Muscle or joint pain	CTRT	9.5	16.9	37.8	25.1	24.5	28.4	23.3	<0.001	0.045	<0.001	0.033	0.19
	RT	7.0	12.6	21.7	17.3	17.2	16.3	16.8					
4. Problems hearing	CTRT	2.5	3.0	11.4	6.8	7.6	10.3	11.5	<0.001	0.24	0.0014	0.049	0.057
	RT	2.2	1.3	4.8	5.1	3.7	5.8	4.1					

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire C30; CTRT = combined chemotherapy and radiotherapy; RT = radiotherapy; CX = cervix; OV = ovarian; HRQOL = health-related quality of life; Tx = treatment; *p* time = changes of quality-of-life scores over time; *p* Tx = difference between the two treatment groups; *p* time by Tx = difference between the two treatment groups over time; *p* Tx at 3 years = difference between the two treatment groups at 3 years; *p* Tx at 5 years = difference between the two treatment groups at 5 years.

* Responses to these questions were only expected if the respondent indicated to be sexually active.

** Responses to this question was only expected if the respondent indicated to have loss of hair.

† Percentages of patients reporting 'a little', 'quite a bit' or 'very much'.

1. Symptom experience subscale; 2. Body image subscale; 3. Sexual functioning subscale; 4. Chemotherapy subscale; 5. Peripheral neuropathy subscale.

Table A3. Characteristics of responders versus non-responders at baseline.

	Non-Responders *n* = 86	Responders *n* = 574	*p*-value
Age at randomization (y)			0.659
<60	36 (41.9)	232 (40.4)	
60-69	32 (37.2)	240 (41.8)	
≥70	18 (20.9)	102 (17.8)	
WHO performance score			**0.001**
0-1	80 (94.1)	567 (99.1)	
2	5 (5.9)	5 (0.9)	
Comorbidities			
Diabetes	12 (14.0)	69 (12.1)	0.748
Hypertension	26 (30.6)	194 (33.8)	0.644
Cardiovascular	9 (10.5)	40 (7.0)	0.363
Country			**<0.001**
The Netherlands	36 (41.9)	102 (17.8)	
United Kingdom	20 (23.3)	157 (27.4)	
Australia & New Zealand	2 (2.3)	116 (20.2)	
France	11 (12.8)	53 (9.2)	
Italy	13 (15.1)	85 (14.8)	
Canada	4 (4.7)	61 (10.6)	
FIGO 2009 stage			0.136
Ia	12 (14.0)	66 (11.5)	
Ib	21 (24.4)	96 (16.7)	
II	15 (17.4)	155 (27.0)	
III	38 (44.2)	257 (44.8)	
Type of surgery			0.681
TAH-BSO	28 (32.6)	163 (28.4)	
TAH-BSO with LND or full staging	36 (41.8)	240 (41.8)	
TLH-BSO	12 (14.0)	76 (13.2)	
TLH-BSO with LND or full staging	10 (11.7)	95 (16.6)	
Radiotherapy			
RT completion	85 (98.8)	569 (99.1)	1.000
Brachytherapy boost	34 (39.5)	275 (48.0)	0.177

Data are *n* (%). FIGO = International Federation of Gynaecology and Obstetrics. EEC = endometrioid endometrial carcinoma. TAH = total abdominal hysterectomy. BSO = bilateral salpingo-oopherectomy. TLH = total laparoscopic hysterectomy. RT = radiotherapy.

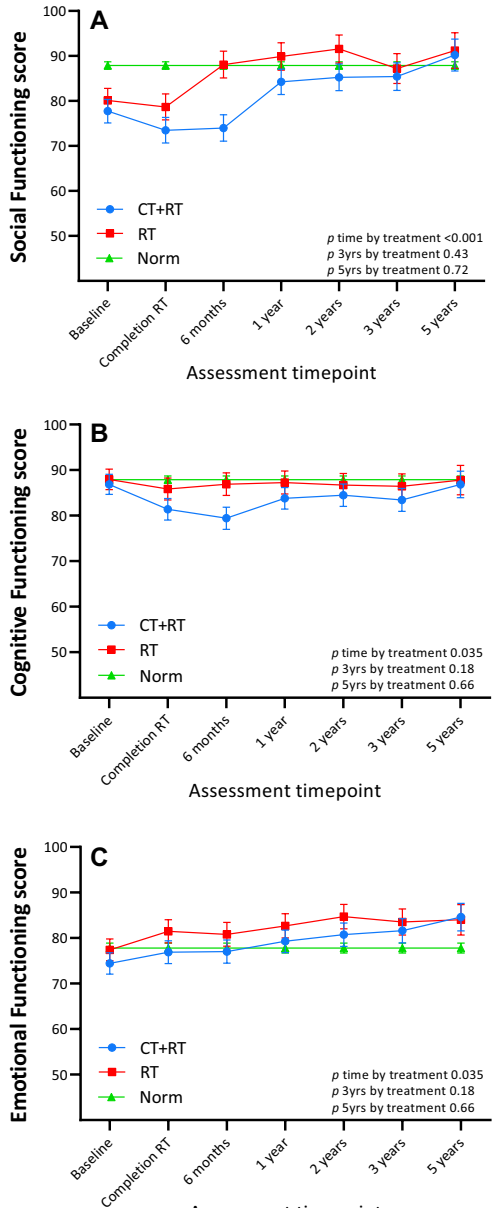


Figure A1. Patient functioning on subscales from EORTC QLQ-C30 for Social functioning (A), Cognitive functioning (B), Emotional functioning (C).

A higher score indicates a higher level of functioning or activity. Error bars show 95% CI. EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; *p* time by treatment = difference between the two treatment groups over time; *p* 3yrs by treatment = difference between the two treatment groups at 3 years; *p* 5yrs by treatment = difference between the two treatment groups at 5 years; CT = chemotherapy; Norm = mean scores of age-match normative data based on women aged 60-69 years across 13 European countries, Canada and the United States;[2] RT = radiotherapy.

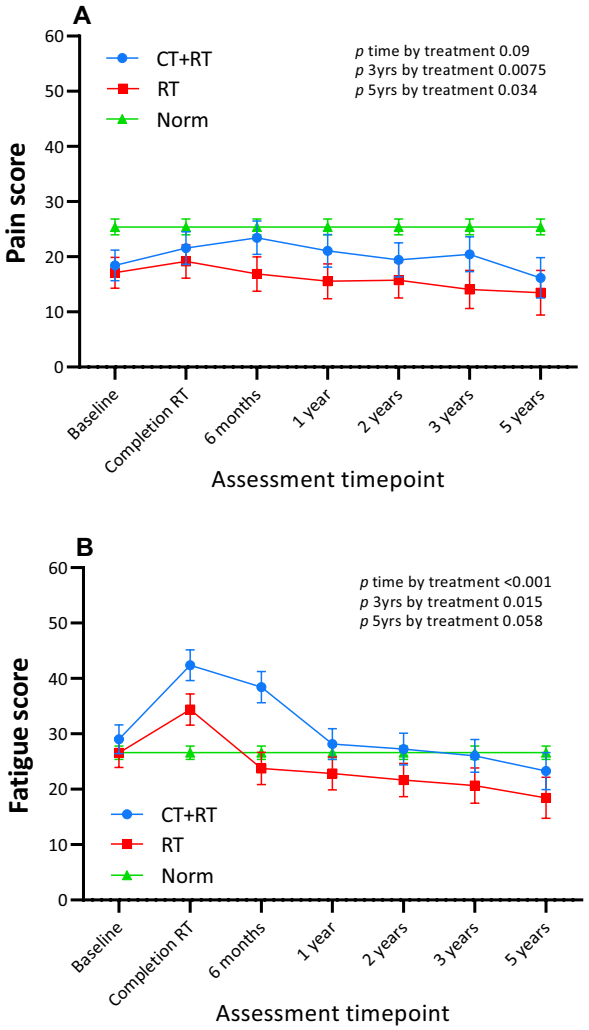


Figure A2. Symptoms scales form EORTC QLQ-C30 for pain (A) and fatigue (B).
A higher score indicates a higher level of symptoms. Error bars show 95% CI. EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; *p* time by treatment = difference between the two treatment groups over time; *p* 3yrs by treatment = difference between the two treatment groups at 3 years; *p* 5yrs by treatment = difference between the two treatment groups at 5 years; CT = chemotherapy; Norm = mean scores of age-match normative data based on women aged 60-69 years across 13 European countries, Canada and the United States;[2] RT = radiotherapy.

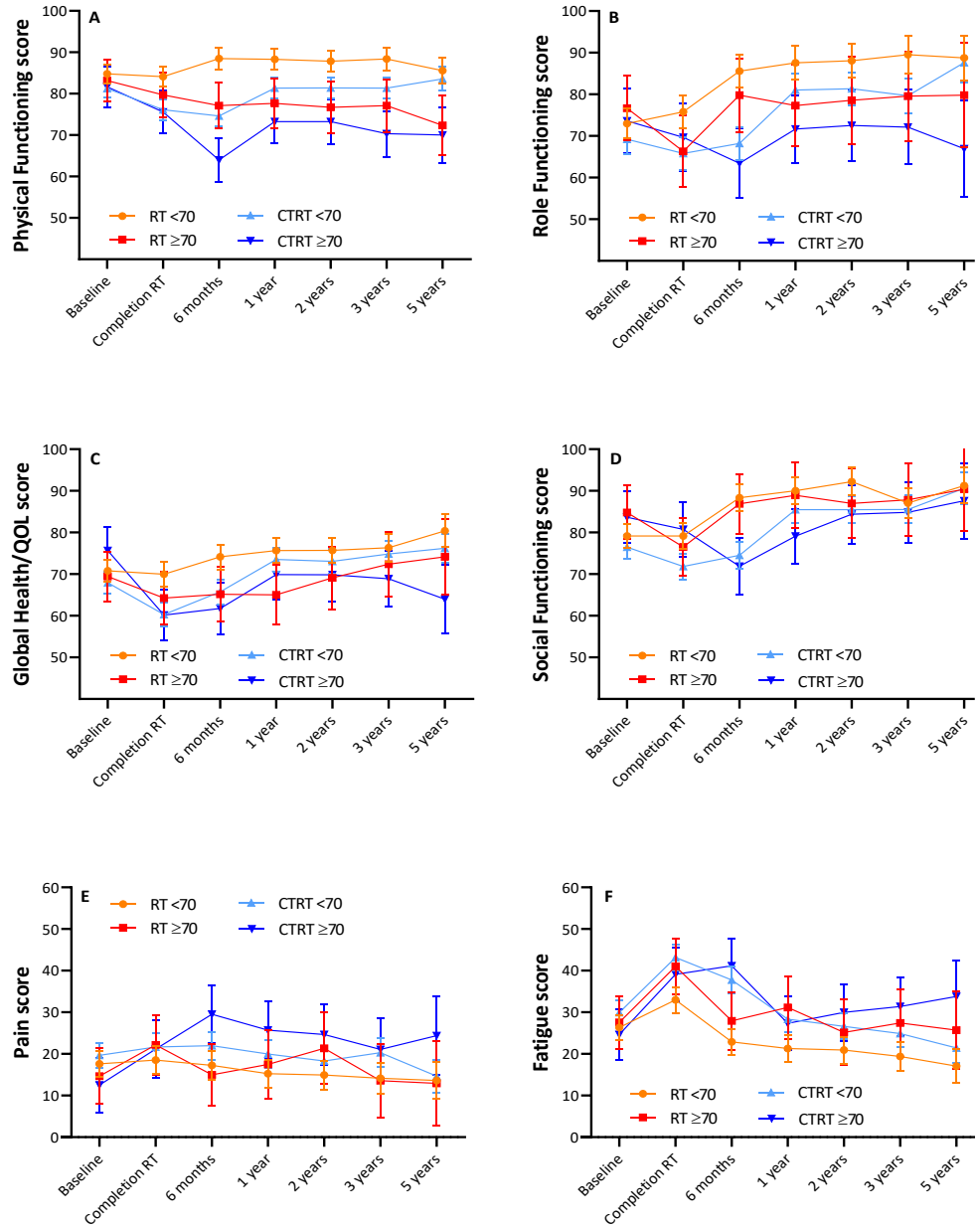


Figure A3. Patient functioning and symptom scales from EORTC QLQ-C30 for physical functioning (A), role functioning (B), global health status/quality of life (C), social functioning (D), pain (E) and fatigue(F). Mean estimates calculated by linear mixed models. For functioning scores (A-D), a higher score indicates a higher level of functioning or activity. For symptom scores (A-B), a higher score indicates a higher level of symptoms. Error bars show 95% CI. EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; <70 = patients aged under 70 years; ≥70 = patients aged 70 years and older; CT = chemotherapy; RT = radiotherapy.

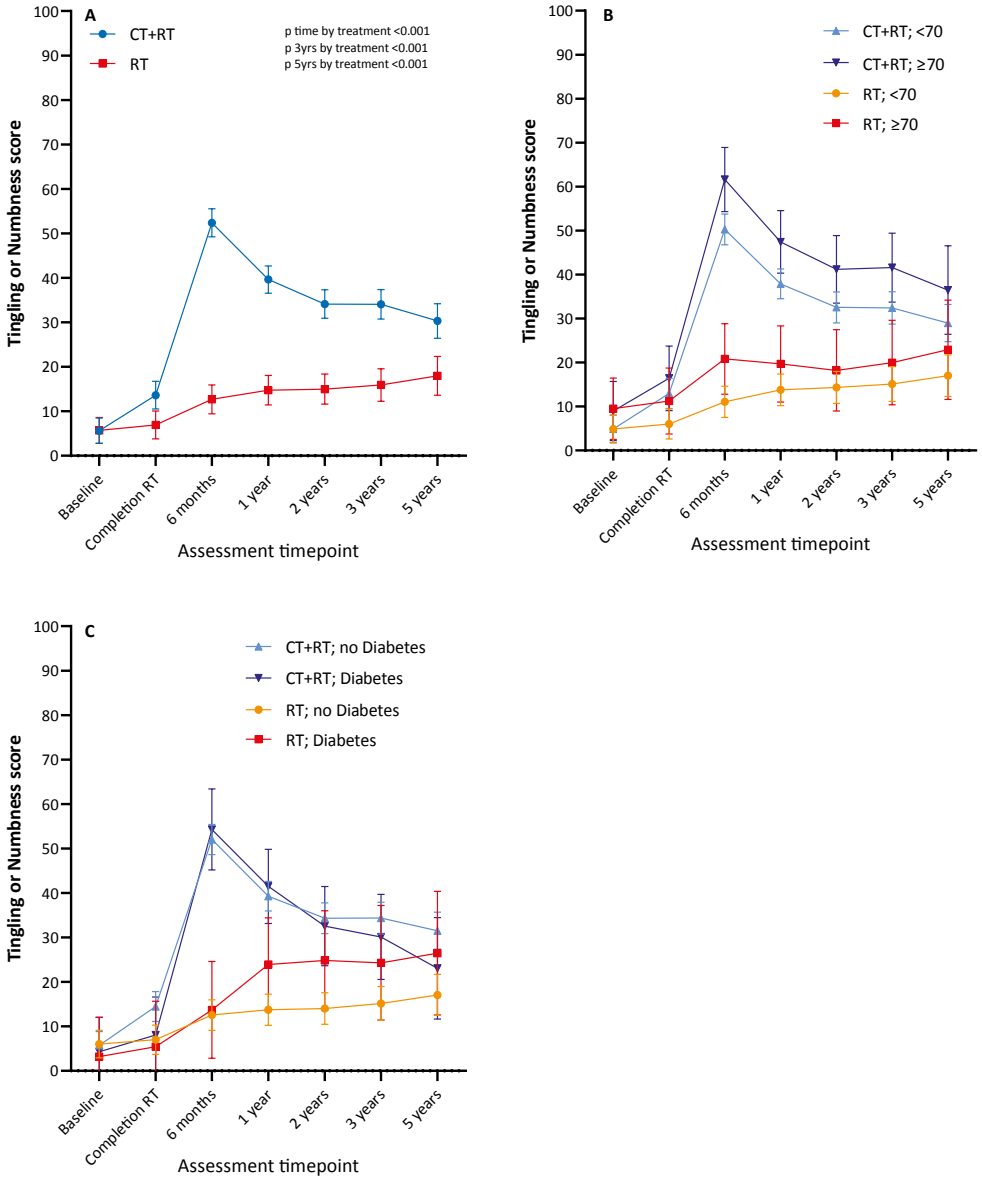
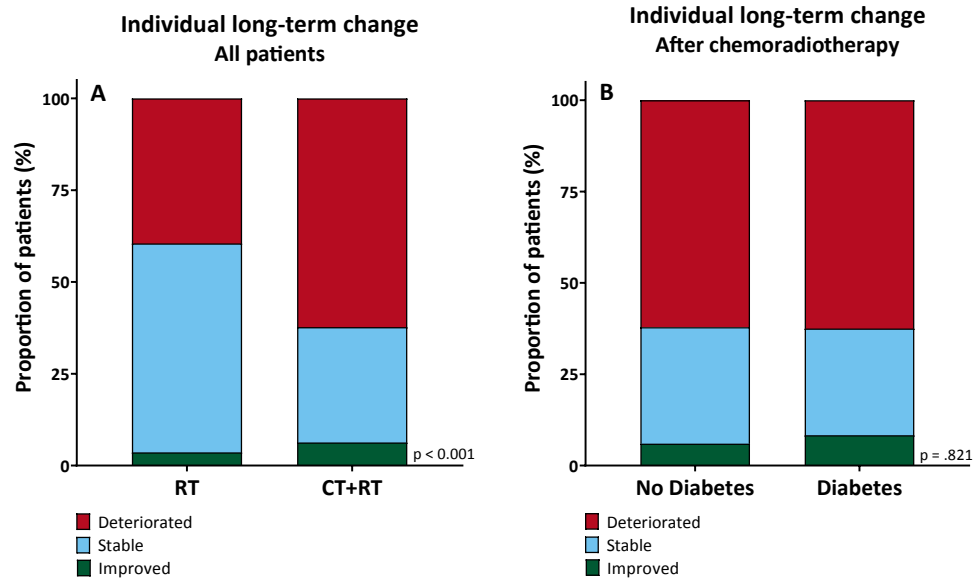


Figure A4. Tingling or numbness item score from EORTC QLQ-CX24 for all patients by received treatment (A) combined with age (B) and diabetes (C).
A higher score indicates a higher level of symptoms. Error bars show 95% CI. EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; <70 = patient age under 70 years; ≥70 = patient age 70 years and older; CT = chemotherapy; RT = radiotherapy.



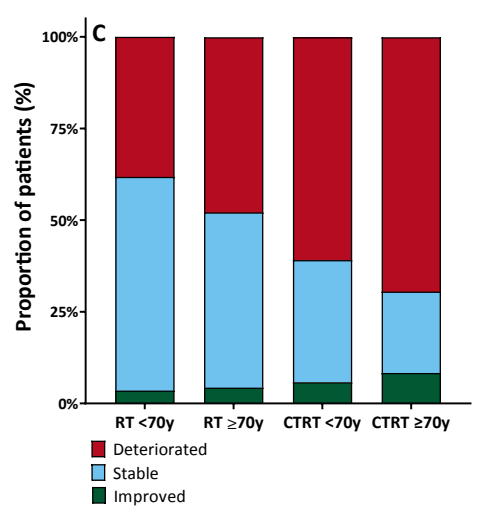


Figure A5. Individual definitive improvement, deterioration or stable state from baseline to long-term (3/5 years) EORTC QLQ-CX24 tingling or numbness item assessment of all patients by received treatment (A), the patients who received chemoradiotherapy by diabetes (B) and all patients by received treatment and age (C).

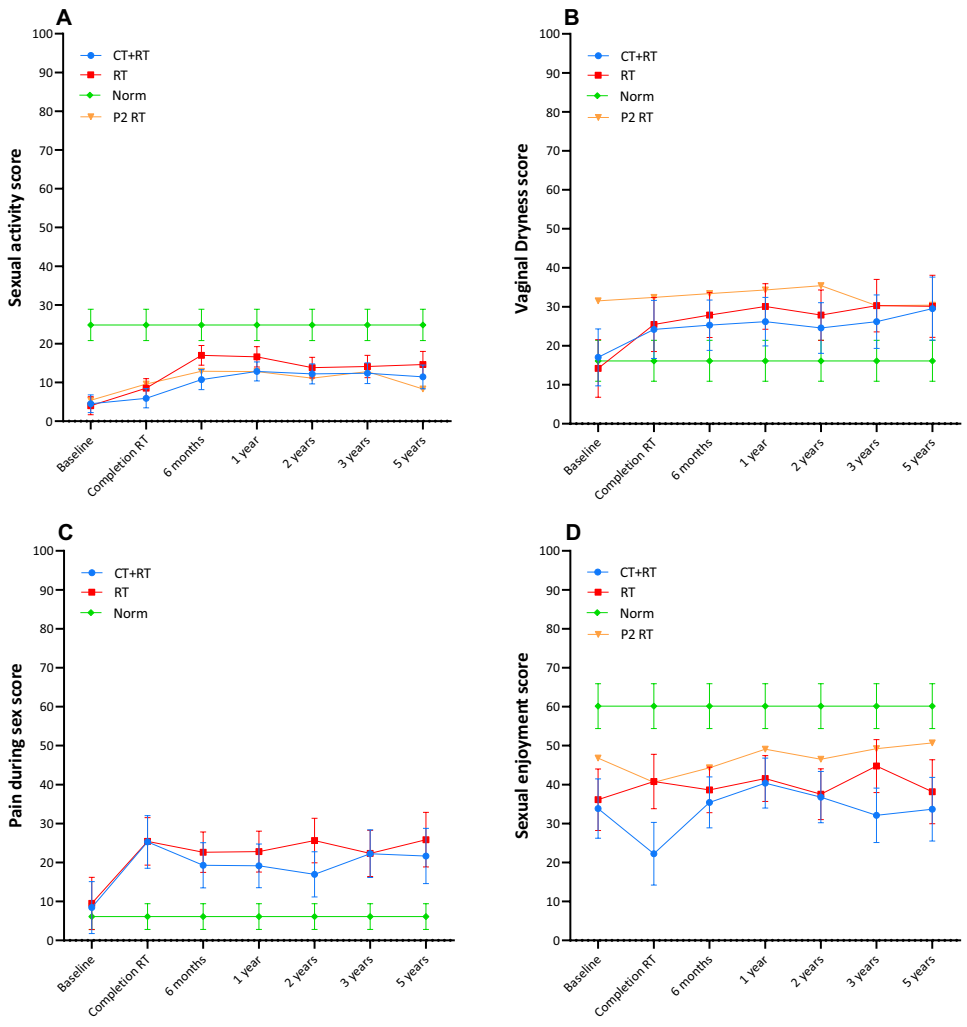


Figure A6. Sexual activity and symptoms scales form EORTC QLQ-CX24 for Sexual activity (A), Vaginal dryness (B), Pain during Sex (C) and Sexual enjoyment (D).

A higher score indicates a higher level of sexual activity and a higher level of symptoms. Error bars show 95% CI. EORTC QLQ-CX24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervix 24 module; CT = chemotherapy; Norm = mean scores of age-match normative data based on Dutch women aged 60-69 years;[3] RT = radiotherapy; P2 RT = pelvic radiotherapy arm of PORTEC-2 trial.[4]

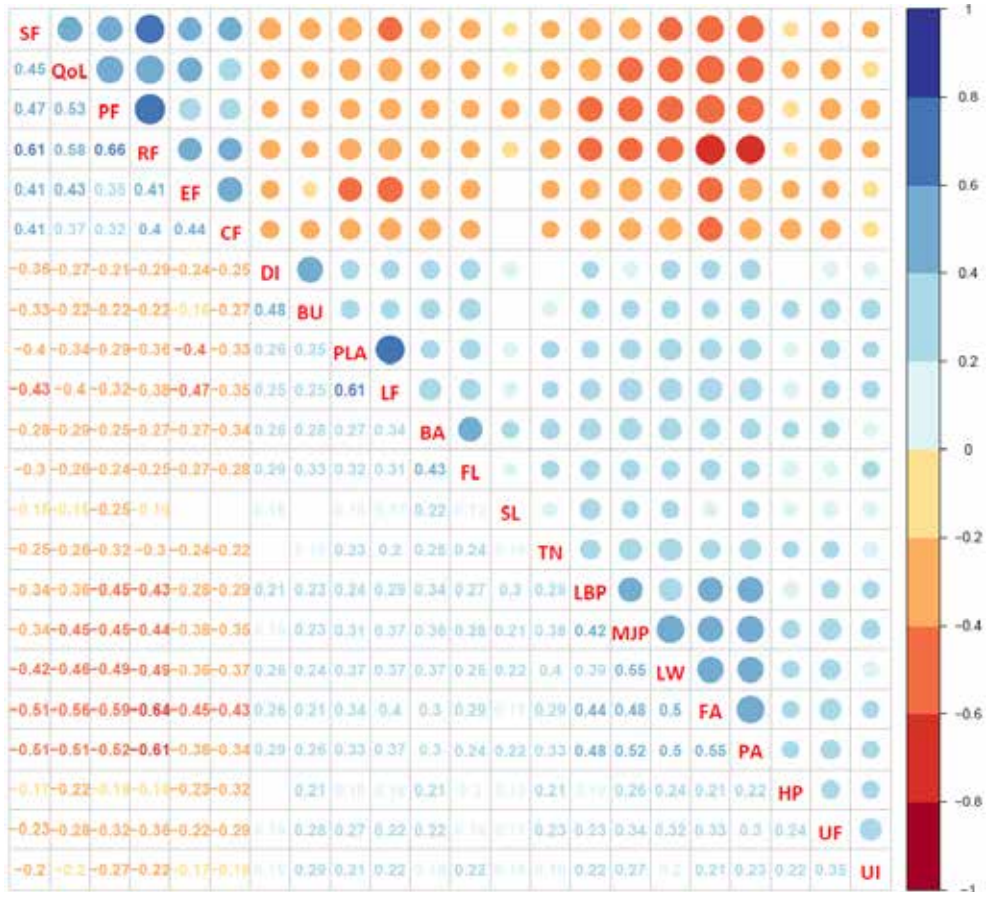


Figure A7. Kendall's rank correlation coefficient matrix of functioning scores and symptom items from EORTC QLQ-C30, CX24 and OV28 at 3/5 years.

Blank regions indicate correlation coefficient (τ) is not significant. Displayed coefficients (τ) are significant at the 0.01 level. SF = Social Functioning; QoL = Global Health/Quality of Life; PF = Physical Functioning; RF = Role Functioning; EF = Emotional Functioning; CF = Cognitive Functioning; DI = Diarrhea; BU = Bowel Urgency; PLA = Feeling Physically Less Attractive; LF = Feeling Less Feminine; BA = Bloated Abdomen; FL = Flatulence; SL = Swollen Legs; TN = Tingling or Numbness; LBP = Lower Back Pain; MJP = Muscle or Joint Pain; LW = Limb Weakness; FA = Fatigue; PA = Pain; HP = Hearing Problems; UF = Urinary Frequency; UI = Urinary Incontinence. Interpretation of τ: The calculations are based on concordant and discordant pairs. For example, suppose patient 1 has a better emotional functioning (ef) than patient 2. If patient 1 also has a better cognitive functioning (cf) than patient 2, the patients have the same relative rank orders and they are concordant pairs with respect to ef and cf. However, if patient 2 has a better cf score, then the patients are discordant pairs. If the number of concordant pairs is much larger than the number of discordant pairs, then the random variables are positively correlated. If the number of concordant pairs is much less than discordant pairs, then the variables are negatively correlated. Finally, if the number of concordant pairs is about the same as discordant pairs, then the variables are weakly correlated. τ = 0.60 means 80% of the pairs are concordant, τ = 0.40 means 70% of the pairs are concordant, τ = 0.20 means 60% of the pairs are concordant (τ = 2 * '% concordant pairs' - 1).

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Chapter 3

Patients' and clinicians' preferences in adjuvant treatment for high risk endometrial cancer: implications for shared decision making

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ABSTRACT

Background

Decision making regarding adjuvant therapy for high risk endometrial cancer is complex. The aim of this study was to determine patients' and clinicians' minimally desired survival benefit to choose chemoradiotherapy over radiotherapy alone. Moreover, influencing factors and importance of positive and negative treatment effects (i.e. attribute) were investigated.

Methods

Patients with high risk endometrial cancer treated with adjuvant pelvic radiotherapy with or without chemotherapy and multidisciplinary gynecologic oncology clinicians completed a trade-off questionnaire based on PORTEC-3 trial data.

Results

In total, 171 patients and 63 clinicians completed the questionnaire. Median minimally desired benefit to make chemoradiotherapy worthwhile was significantly higher for patients versus clinicians (10% vs 5%; $p = .02$). Both patients and clinicians rated survival benefit most important during decision making, followed by long-term symptoms. Older patients (OR 0.92, 95% CI 0.87–0.97; $p = .003$) with comorbidity (OR 0.34, 95% CI 0.12–0.89; $p = .035$) had lower preference for chemoradiotherapy, while patients with better numeracy skills (OR 1.2, 95% CI 1.05–1.36; $p = .011$) and chemoradiotherapy history (OR 25.0, 95% CI 8.8–91.7; $p < 0.001$) had higher preference for chemoradiotherapy.

Conclusions

There is a considerable difference in minimally desired survival benefit of chemoradiotherapy in high risk endometrial cancer among and between patients and clinicians. Overall, endometrial cancer patients needed higher benefits than clinicians before preferring chemoradiotherapy.

Introduction

Endometrial cancer is the most common gynecological malignancy in developed countries. Although most women with endometrial cancer are diagnosed at early stage of disease, 15–20% are diagnosed with high risk disease with increased incidence of recurrence and cancer-related death. The PORTEC-3 trial investigated the treatment effect of combined adjuvant pelvic radiotherapy and chemotherapy versus pelvic radiotherapy alone for women with high risk endometrial cancer. The updated survival analysis showed a 5-year overall survival (OS) benefit of 5% (81% vs 76%, HR 0.70, $p = 0.034$) and failure-free survival benefit of 7% (76% vs 69%, HR 0.70, $p = 0.016$) with chemoradiotherapy as compared to radiotherapy alone, with the greatest benefit of 10% or more observed in women with serous cancers and those with stage III disease.[1] Toxicity is most frequent and severe during treatment, but the lower grade toxicities, which may have long-term impact, should not be neglected. Pelvic radiotherapy is associated with higher risks of long-term gastrointestinal and genitourinary symptoms, with impact on physical and role functioning.[2, 3] Adding chemotherapy leads to additional symptoms that may persist (e.g. persisting tingling or numbness of hands or feet reported by 25% of the patients at 3 and 5 years after treatment, and a small deterioration in physical and role functioning during the first 3 years after treatment).[4] Weighing these pros and cons reflects the complexity of shared decision-making on adjuvant treatment for patients with high risk endometrial cancer.

The current analysis was initiated to investigate preferences of women with high risk endometrial cancer and multidisciplinary clinicians. The actual differences in survival and symptoms were presented, in order to determine which benefit exceeded the risks sufficiently to consider the addition of chemotherapy to radiotherapy worthwhile in women with high risk endometrial cancer. In addition, factors influencing the decision and the importance assigned to the major positive and negative treatment outcomes were investigated.

Participants and methods

Study population and procedures

For the patient study, patients with high risk endometrial cancer were enrolled in 12 radiation oncology centers across the Netherlands. Selection criteria were: surgery with curative intent with adjuvant pelvic radiotherapy with or without chemotherapy; treated after 2014; alive without recurrent disease reported until last follow-up; no other cancer; able to read Dutch. Because of the pragmatic nature of the study and the fact that the indication of adjuvant pelvic radiotherapy is limited to endometrial cancer with high risk

features we used diagnosis and treatment codes for selecting patients from the hospital databases. Patients were approached via their treating radiation oncologist by letter. Patients were asked to fill out a self-administered web-based questionnaire. On request, a paper version was available. An anonymized approach without linked patient report data was used, therefore no reminders could be sent. We pilot-tested the questionnaire in a sample with varied medical history across the Netherlands.

For the clinician study, we approached multidisciplinary gynecologic oncology clinicians (including radiation oncologists, gynecologic oncologists and medical oncologists) via the Dutch Gynecologic Oncology Group. Clinicians were approached via email with a link to the web-based questionnaire. After two weeks clinicians received a reminder. Question validation was enabled in the web-based questionnaire to prevent missing values. The Medical Ethics Committee of Leiden University Medical Centre approved the study.

Measures

For the patient study, clinical factors (cancer treatment history and any comorbidities influencing daily life) and sociodemographic factors, health literacy[5] and numeracy[6], treatment preferences and attribute importance ratings were assessed (Appendix A1 displays the health literacy and numeracy questions). For the clinician study, sociodemographic factors, affiliation and main specialty, treatment preferences and attribute importance ratings were assessed.

Participants' minimally desired 5-year overall survival benefit (MDSB) from chemoradiotherapy as compared to radiotherapy alone was assessed using the treatment trade-off method.[7] Patients and clinicians were asked to imagine that they had recently been diagnosed with high risk endometrial cancer and that their clinician offered them two treatment strategies. We made explicit that the situation was hypothetical and did not refer to their individual situation. Based on known data from the quality of life analysis of the PORTEC-3 trial, an overview with the most frequent symptoms and deterioration in functioning was presented (available in Appendix A2). The importance assigned to every treatment outcome (attribute) was rated using a 4-point Likert-type response scale. Subsequently, participants were asked what treatment option they preferred at a 5% benefit of additional chemotherapy. If they chose radiotherapy alone, the survival benefit with addition of chemotherapy varied with 5% increments to a maximum benefit of 25% over the baseline of 75% until they switched their preference. When participants had chosen chemoradiotherapy at 5% or 10% survival benefit, they were asked for their MDSB (multiple choice question ranging between 1 and 5% or 6 and 10%, respectively).

Statistical analysis

Empty returned questionnaires, those with information on characteristics only, and those with inconsistent answers among the trade-off questions were excluded for analysis as displayed in Figure 1. The analysis was primarily descriptive. Categorical variables were compared using Fisher's exact test or chi-square test. Continuous and ordinal variables were compared using Mann-Whitney *U* test or Kruskal-Wallis test. The following groups were compared: (A) patients versus clinicians, (B) patients previously treated with adjuvant radiotherapy alone versus chemoradiotherapy, (C) the three clinician specialties.

Univariable and multivariable logistic regression with likelihood-based backward selection were performed to identify predictors for chemoradiotherapy preference at a 5% survival benefit.

A two-sided *p*-value ≤0.05 was considered statistically significant for the treatment trade-off and logistic regression. For comparison of attribute importance ratings, a two-sided *p*-value ≤0.01 was considered statistically significant and ≤0.05 was considered a trend to guard against false-positive results due to multiple testing. Statistical analyses were done with R version 3.6.1.

Results

In total, 453 eligible patients were approached. Of these patients, 205 (45%) started the questionnaire, of which 171 (83%) were evaluable (131 online (77%) and 40 paper (23%); Fig. 1). Among the 106 clinicians approached, 63 (59%; 21/39 radiation oncologists, 34/54 gynecologic oncologists, and 8/13 medical oncologists) completed the online questionnaire. Table 1 shows the baseline characteristics for both patients and clinicians.

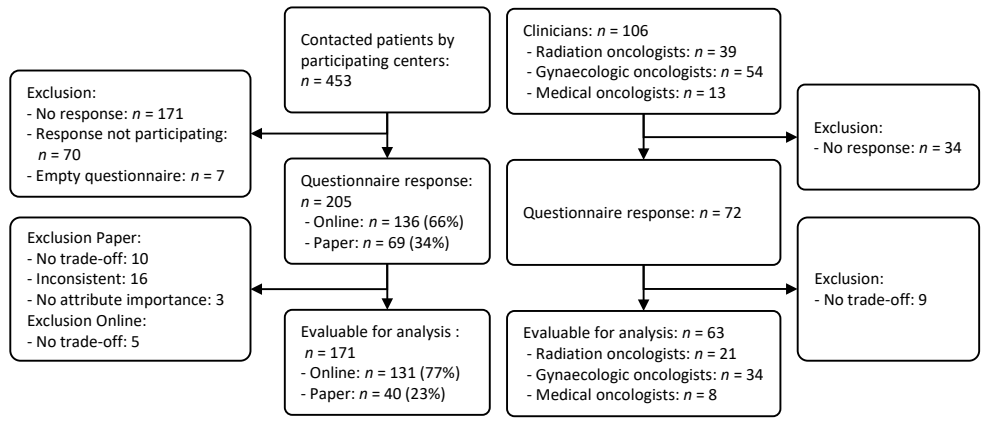

Figure 1. Flowchart

Median Subjective Numeracy Scale score was 14 (IQR 11–16) on a scale from 3 to 18 with larger scores indicating a higher subjective rating of numeracy. Median literacy score was 6 (IQR 5–7) on a scale from 0 to 12 with higher scores reflecting greater problems with reading.

Treatment preference and minimally desired survival benefit

At a 5% survival benefit, 69 (40%) of the patients and 41 (65%) of the clinicians preferred chemoradiotherapy over radiotherapy alone ($p = 0.001$). In Table 2 the MDSB ratings are listed. Figure 2 shows the cumulative proportion of participants preferring chemoradiotherapy according to MDSB. Overall, the median MDSB for preferring chemoradiotherapy was significantly higher for patients than for clinicians (10% vs 5%, $p = 0.024$). Patients who had received chemoradiotherapy had a significantly lower MDSB than patients who had received radiotherapy alone (2% vs 10%, $p < 0.001$). There was no significant difference between the clinician specialties ($p = 0.46$).

Table 1. Participant characteristics

Patients	***n* = 171**
Age, years (median [IQR])	67 [60-72]
Marital status (%)	
Married/Living together	100 (58.5)
Partner, living alone	6 (3.5)
No partner/widow	65 (38.0)
Having children = Yes (%)	121 (70.8)
Educational level (%)	
Low	69 (40.4)
Intermediate	49 (28.7)
High	50 (29.2)
Other	3 (1.8)
Main daily activity (%)	
Paid/unpaid job	54 (31.6)
Leisure and IADLS	117 (68.4)
Comorbidity = Yes (%)	123 (71.9)
Received radiotherapy (%)	
EBRT	95 (56.2)
EBRT+VBT	69 (40.8)
VBT	5 (3.0)
Chemotherapy = Yes (%)	42 (24.6)
Time since diagnosis in, years (median [IQR])	3 [2-5]

Clinicians	***n* = 63**
Age, years (median [IQR])	50 [43-56]
Sex (%)	
Male	16 (25.4)
Female	47 (74.6)
Specialty (%)	
Radiation oncology	21 (33.3)
Gynecologic oncology	34 (54.0)
Medical oncology	8 (12.7)
Current institution (%)	
General	28 (44.4)
Academic	25 (39.7)
Categorical	10 (15.9)
Number of EC patients per month (median [IQR])	4 [2-5]

Education level: low = elementary school, completed lower general secondary education/vocational training; intermediate: higher secondary educational/vocational training; high = higher professional education, university, doctor; EBRT = external beam radiotherapy; EC = endometrial cancer; IADLS: instrumental activities of daily living; VBT = vaginal brachytherapy.

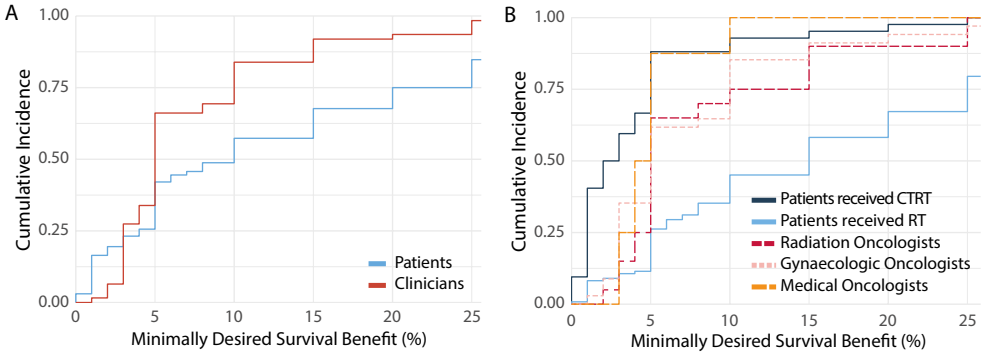

Figure 2. Cumulative proportion of participants preferring chemoradiotherapy over radiotherapy alone according to minimally desired survival benefit by patients versus clinicians (A) and their subgroups (B). Baseline 5-year survival rate with radiotherapy alone is 75%. The maximum survival benefit is 25% corresponding to a 5-year survival rate of 100%. Numbers do not add up to 1.00 because of those declining chemoradiotherapy irrespective of any survival benefit. CTRT = chemoradiotherapy; RT = radiotherapy.

Table 2. Minimally desired survival benefit (MDSB) from chemoradiotherapy

		Percentile					
	MDSB	**25th**	**75th**	**5th**	**95th**	**NA**	***p*-value**
							0.024*
Patients (*n*=171)	10	4	20	1	infin.	7	<0.001†
Received Pelvic Radiotherapy (n=129)	15	5	25	1	infin.	7	
Received Chemoradiotherapy (n=42)	2	1	5	0	15		
Clinicians (*n*=63)	5	3	10	2	25	1	0.46†
Radiation oncologists (n=21)	5	4	10	2	25	1	
Gynecologic oncologists (n=34)	5	3	10	2	20		
Medical oncologists (n=8)	4	3	5	3	10		

p values less than or equal to 0.05 were deemed significant

*Between group comparison: patients versus clinicians; †Within group comparison

Attribute importance

Figure 3 shows the distribution of importance assigned to each attribute by patients and clinicians. Survival benefit was judged as the most important attribute, followed by the long-term symptoms (i.e. '25% with persistent tingling/numbness', and 'small decline in physical functioning'), both by patients and clinicians. There was a trend for patients judging moderate deterioration in physical functioning during treatment more important ($p = 0.025$) and persistent tingling/numbness less important ($p = 0.027$) than clinicians. The treatment duration was judged as least important, especially by clinicians (judged as not important by 30% of patients vs 43% of clinicians, $p < 0.001$). Patients considered diarrhea ('36% during treatment for both treatment groups'; $p = 0.001$) and social functioning during treatment ('moderate deterioration'; $p = 0.003$) more important in their decision than clinicians.

Patients who had received chemoradiotherapy judged treatment duration less important than those who had received radiotherapy alone (judged as not important by 55% [CTRT] vs 22% [RT], $p < 0.001$), as well as hair loss during treatment (36% vs 16%, $p = 0.003$). In addition, there was a trend for several other negative attributes to be judged less important by patients who had received chemoradiotherapy (Appendix Figure B1). There were no statistically significant differences in attribute importance between the three clinician specialties. However, there was a trend for different ratings of short-term fatigue and quality of life, and short- and long-term functioning importance, with radiation oncologists rating these attributes of higher importance than other specialists ($p < 0.05$; Appendix Figure B2).

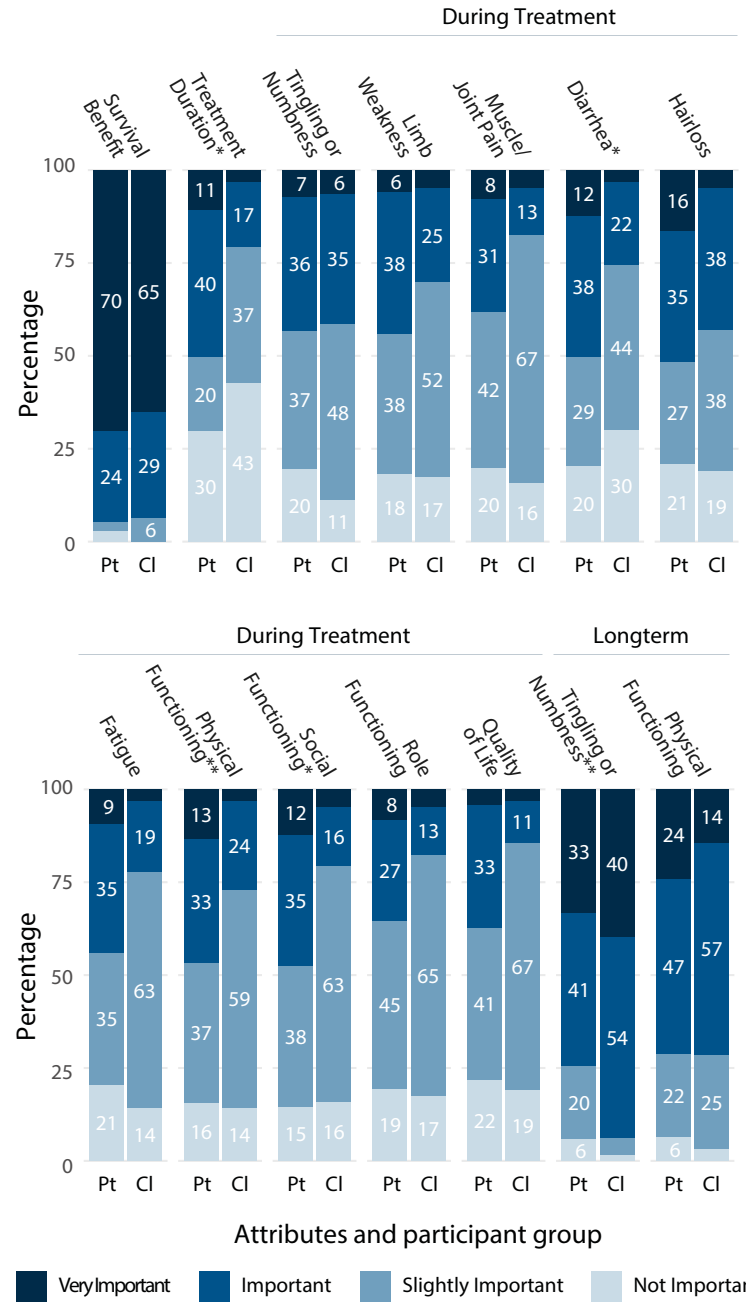

Figure 3. Attribute importance ratings in decision making

Attribute importance ratings in the decision between chemoradiotherapy and radiotherapy alone after reading the trade-off overview with a 5% survival benefit. Pt = patients; Cl = clinicians.

*p value less than or equal to 0.01 shows significance; **p value less than or equal to 0.05 shows a trend.

Factors influencing treatment preference

Multivariable logistic regression showed that patients with an older age (OR 0.92, 95% CI 0.87–0.97; $p = 0.003$) and comorbidity (OR 0.34, 95% CI 0.12–0.89; $p = 0.035$) were less likely to prefer chemoradiotherapy, while those with a higher subjective numeracy score (OR 1.2, 95% CI 1.05–1.36; $p = 0.011$) and a chemoradiotherapy history (OR 25.0, 95% CI 8.8–91.7; $p < 0.001$) were more likely to prefer chemoradiotherapy over radiotherapy alone (Table 3). For clinicians, none of baseline variables entered in the multivariable logistic regression model were statistically significant predictors (data not shown).

Table 3. Predictors of preference for chemoradiotherapy at a 5% survival benefit among patients

	Univariable logistic regression				Multivariable logistic regression			
	OR	**Lower 95% CI**	**Upper 95% CI**	***p***	**OR**	**Lower 95% CI**	**Upper 95% CI**	***p***
Age	0.92	0.88	0.96	<0.001	0.92	0.87	0.97	0.003
Comorbidity (Yes vs No)	0.35	0.15	0.73	0.007	0.34	0.12	0.89	0.035
Received CTRT (Yes vs No)	26.3	9.59	93.1	<0.001	27.5	9.22	106	<0.001
Subjective Numeracy Scale	1.13	1.03	1.24	0.015	1.18	1.05	1.36	0.011

p values less than or equal to 0.05 were deemed significant

CTRT = chemoradiotherapy; IADLS = instrumental activities of daily living; OR = odds ratio for chemoradiotherapy preference in the decision between chemoradiotherapy and radiotherapy alone after seeing the trade-off overview with a 5% survival benefit; 95% CI = 95% confidence interval.

Discussion

This patient preference study for high risk endometrial cancer showed that patients desired higher survival benefits than clinicians before preferring adjuvant chemoradiotherapy over radiotherapy alone. The minimally desired survival benefit varied considerably among both patients and clinicians. Patients' preferences were strongly influenced by treatment history. In addition, younger age, having no comorbidities and higher subjective rating of numeracy were predictors of the preference for chemoradiotherapy. Survival benefit was judged to be the most important attribute in decision making by both patients and clinicians, followed by the risk of developing long-term symptoms (i.e. neuropathy and impaired physical functioning).

Patients had a median MDSB of 10% over the baseline 5-year survival rate of 75% with radiotherapy alone, while clinicians had a median MDSB of 5% to make adjuvant chemoradiotherapy worthwhile. It was unexpected that we found different results compared to those of the previous patient preference study related to the PORTEC-3 trial. The ANZGOG sub-study among 83 high risk endometrial cancer patients recruited to the PORTEC-3 trial found that patients, compared to clinicians, desired lower benefits to make

chemoradiotherapy worthwhile (4% vs 10% over a 5-year survival rate of 65%).[8] Having encountered the symptoms and adverse events of patients, but particularly knowing the results of the PORTEC-3 trial (5% benefit) may have made the clinicians in our study less reluctant in accepting chemotherapy for a small benefit. The relatively low survival benefit desired among patients in the ANZGOG sub-study may be explained by the selection of patients who had decided to take part in the PORTEC-3 trial and thus were likely to accept chemotherapy for an uncertain benefit. Meanwhile, patient preferences in our study were influenced by treatment history, and most patients (75%) did not receive chemotherapy.

The variability of MDSB was high, although the range among clinicians was slightly narrower than among patients. This high variability in preferences has been reported by others as well.[8-10] Younger age, having no comorbidity and better numeracy skills were predictive for preferring chemoradiotherapy in our study, while most studies report a lack of predictors. Nevertheless, individual treatment preferences remain hard to predict from baseline characteristics, and are most likely influenced by a complex of experiences, values and attitudes. Treatment preferences are clearly influenced by actual treatment received. Many studies have reported that patients who are about to undergo treatment or have experienced a treatment generally adapt to their decision by having stronger preference for that treatment.[9, 11, 12] This is a known psychologic process to make preferences agree with the preceding decision called cognitive dissonance reduction or cognitive justification. In the shared decision making process, it may be helpful to explore the patient's prior experience with the treatments considered, e.g. in close family members, and discuss the potential bias this may have caused.

We did not find a significant difference in MDSB between clinicians from different specialties. Previous research reported that clinicians generally need less benefit from the treatment of their own specialty.[9, 13, 14] The fact that this was not found in our study may be explained by the small number of medical oncologist, multidisciplinary treatment approach in current practice and knowledge of the PORTEC-3 trial results.

The most important attribute in decision making, for both patients and clinicians, was survival benefit. This has been reported in several cancer preference studies.[15, 16] However, thorough evaluation of multiple attributes, especially with distinction of short-term and long-term impairments, is novel. Some studies emphasized the importance of quality of life in general, but without detailed attributes.[16, 17] We found that the risk of developing long-term symptoms (i.e. neuropathy and impaired physical functioning) is of high importance to patients. While treatment duration was considered the least important attribute, all short-term symptoms and impairments were of intermediate importance.

There were clear strengths to our study. First, many patients across our entire country participated to represent the Dutch high risk endometrial cancer population. This, together with the relative large sample size allowed subgroup analysis and multivariable logistic regression. Second, the presented information on survival and long-term symptoms were based on the actual data of the randomized PORTEC-3 trial, ensuring a reliable representation of clinical practice. In addition, the novelty of our study was enhanced by allowing a thorough analysis of attribute importance. Third, the web-based questionnaire design prevented interviewer introduced bias, facilitated response, allowed direct comparison between patients and clinicians, and provided complete data.

The main limitation of our study was the inability to include patients at the moment they were actually facing the treatment decision. Our results were clearly influenced by the preceding treatment. Selecting only disease-free patients may have reinforced this influence. Generally, patients without recurrence are more satisfied with care than patients with recurrence.[18] In addition, we did not have details on the patient's persistent symptoms, which may be influencing preference as well. Lastly, response bias may have occurred. Due to the non-random sample and the lack of information on patients who did not complete the questionnaire, we are unable to correct for this potential bias.

Clinical implications of this study are knowledge of the variability of preferences among endometrial cancer patients facing the treatment decision for adjuvant chemoradiotherapy, and of the differences between clinicians and patients. Therefore, detailed discussion about the benefits and harms are necessary to ensure their decisions are well informed and aligned with their personal values, attitudes and priorities, and not unduly influenced by clinician preferences. Clinicians tend to underestimate patients preference for less toxic treatments.[19, 20] As reinforced by this study, it is important to realize that patients might not be as willing to undergo chemotherapy as clinicians themselves. In addition, it would be important to realize that patients highly value clinicians' recommendations and that recommendations may lead people to make decisions that ultimately go against what they would otherwise prefer.[21] With the actual 5% overall survival difference in the PORTEC-3 trial[1], only 40% of the patients and 63% of clinicians would prefer adjuvant chemoradiotherapy over radiotherapy alone. Based on a survival benefit of 10% or more, adjuvant chemoradiotherapy is only advised for women with stage 3 disease and those with serous or p53 abnormal endometrial cancer.[1, 22] Our study showed that with this benefit, 57% of the patients and 84% of the clinicians would prefer adjuvant chemoradiotherapy.

Our results on attribute importance can guide patient information. It is important to point out the possibility of long-term symptoms. Patients should be informed about the expected

toxicity due to standard adjuvant pelvic radiotherapy before making a decision, even if the risk is equal when adding adjuvant chemotherapy (e.g. 36% risk of diarrhea). Although individually not significant, patients rated most negative attributes more important than clinicians. Meanwhile, clinicians seem to rate long-term tingling/numbness higher than patients. Clinicians may imagine the accompanied burden they have seen in practice resulting in higher attribute values, while the terms 'tingling', 'numbness' or 'neuropathy' might be abstract for patients without knowledge or experience. Therefore, it is important that clinicians ask about hobbies and other social activities that might be impacted and give practical examples to make it more imaginable.

In conclusion, our results showed considerable differences in minimally desired survival benefit to make adjuvant chemoradiotherapy in high risk endometrial cancer worthwhile, both among and between patients and clinicians. Overall, endometrial cancer patients desired higher survival benefits than clinicians before preferring chemoradiotherapy.

Acknowledgements

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APPENDIX A

A1. health literacy and numeracy

Health literacy

The following 3 health literacy screening questions were included:

(1) "How often do you have someone (like a family member, friend, hospital/clinic worker or caregiver) help you read hospital materials?" (Help Read);
(2) "How often do you have problems learning about your medical condition because of difficulty understanding written information?" (Problems Reading);
(3) "How confident are you filling out forms by yourself?" (Confident with Forms).

Participants were asked to choose between all of the time, most of the time, some of the time, a little of the time or none of the time. Answers were translate to a score on a scale from 0 to 4. The SNS score was calculated by summing up the three scores (range 0-12). A higher score indicates greater problems with reading.

Reference: Chew LD, Griffin JM, Partin MR et al. Validation of Screening Questions for Limited Health Literacy in a Large VA Outpatient Population. Journal of General Internal Medicine 2008; 23: 561-566.

Health numeracy

The shortened SNS-3 consisted of the following items each on a 6-point Likert scale, with interior responses labeled by numbers 2 through 5:

(1) How good are you at working with fractions? ("Not good at all," to "Extremely Good,");
(2) How good are you at figuring out how much a shirt will cost if it is 25% off? ("Not good at all," to "Extremely Good,");
(3) How often do you find numerical information to be useful? ("Never" to "Very Often,").

The first two questions focus on self-reported numeracy skills ("fractions" and "shirt"), while the third focuses on subject preference ("useful"). The SNS score was calculated by summing up the three answers (range 3-18). A higher score indicates a higher subjective rating of numeracy abilities and preferences.

Reference: McNaughton CD, Cavanaugh KL, Kripalani S et al. Validation of a Short, 3-Item Version of the Subjective Numeracy Scale. Med Decis Making 2015; 35: 932-936.

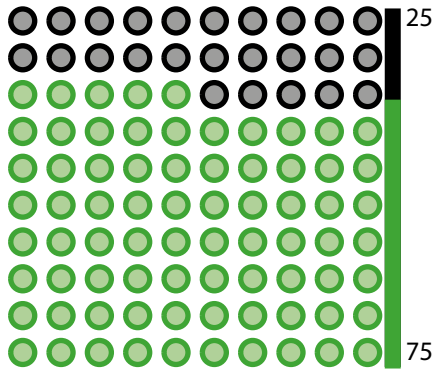
A2. treatment trade-off overview

The following overview represents the positive and negative attributes shown to participants in the treatment trade-off. After this overview with textual explanation participants had to answer the trade-off questions.

Positive attributes

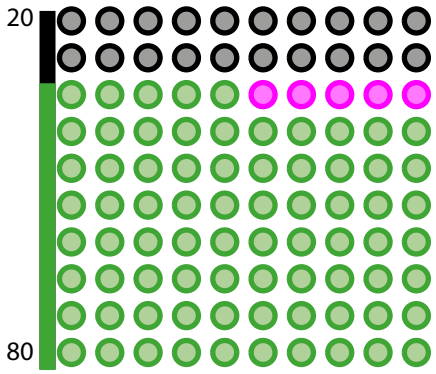
Survival benefit

Radiotherapy alone



25 out of 100 patients deceased
75 out of 100 patients alive

Chemoradiotherapy

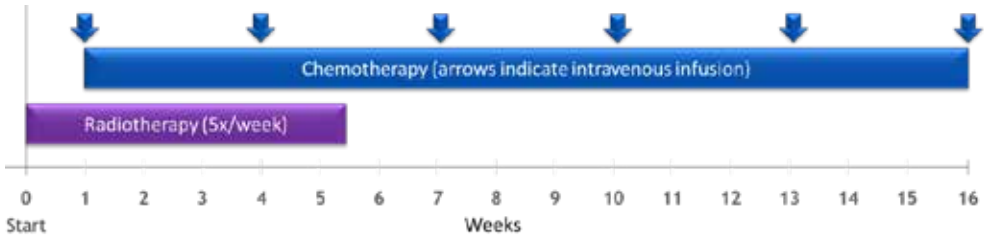


20 out of 100 patients deceased
80 out of 100 patients alive

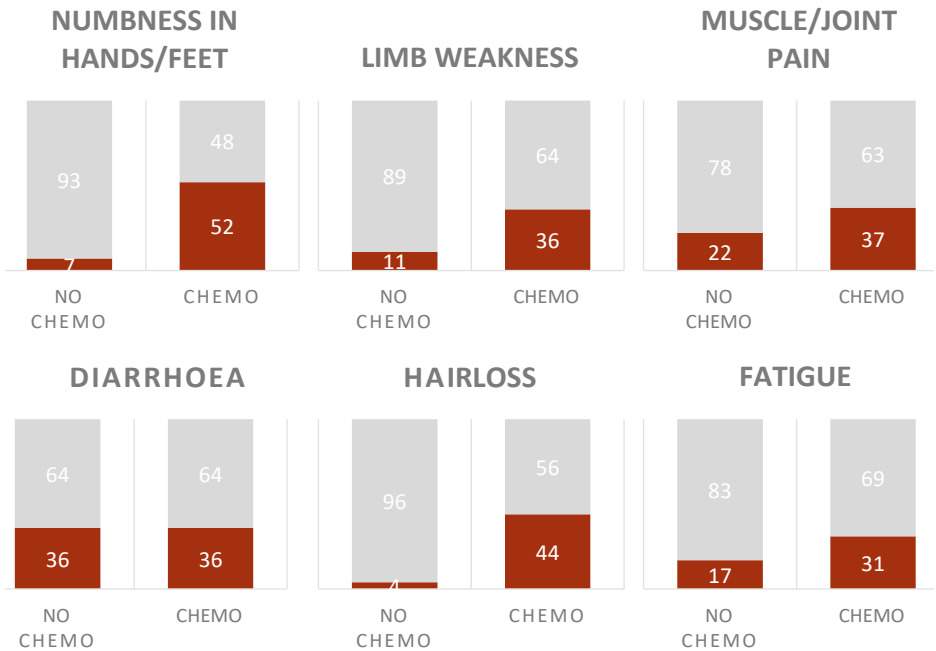
Survival at 5 years post-treatment. Green = alive; Pink = chemotherapy induced survival; Black = deceased.

Negative atributes

Treatment duration



Symptoms and functioning during and shortly after treatment



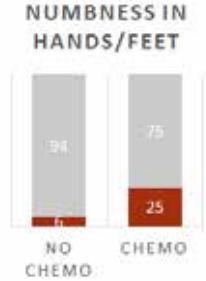
Example: During and shortly after chemotherapy, 52 out of 100 patients experienced tingling or numbness in hands and/or feet, compared to 7 patients in the radiotherapy group.

Effects on functioning and quality of life during treatment with chemoradiotherapy compared to patients treated with radiotherapy alone. Addition of chemotherapy causes:

- A small deterioration in quality of life;
- A moderate deterioration in physical functioning (exertion and daily activities);
- A moderate deterioration in social activities and family life;
- A moderate deterioration in daily activities (work/hobbies);
- No difference in memory/thinking and emotional functioning.

Long term symptoms and functioning impairments caused by CTRT

- After 3 years, 1 out of 4 patients experiences quite a bit or very much tingling or numbness in hands/feet;
- After 3 years, patients have a small decline in physical functioning;
- These symptoms have improved compared to during/shortly after treatment;
- After 3 years, other symptoms and influence on functioning have been recovered to a large extend. There are no differences between patients that did or did not receive chemotherapy.



APPENDIX B

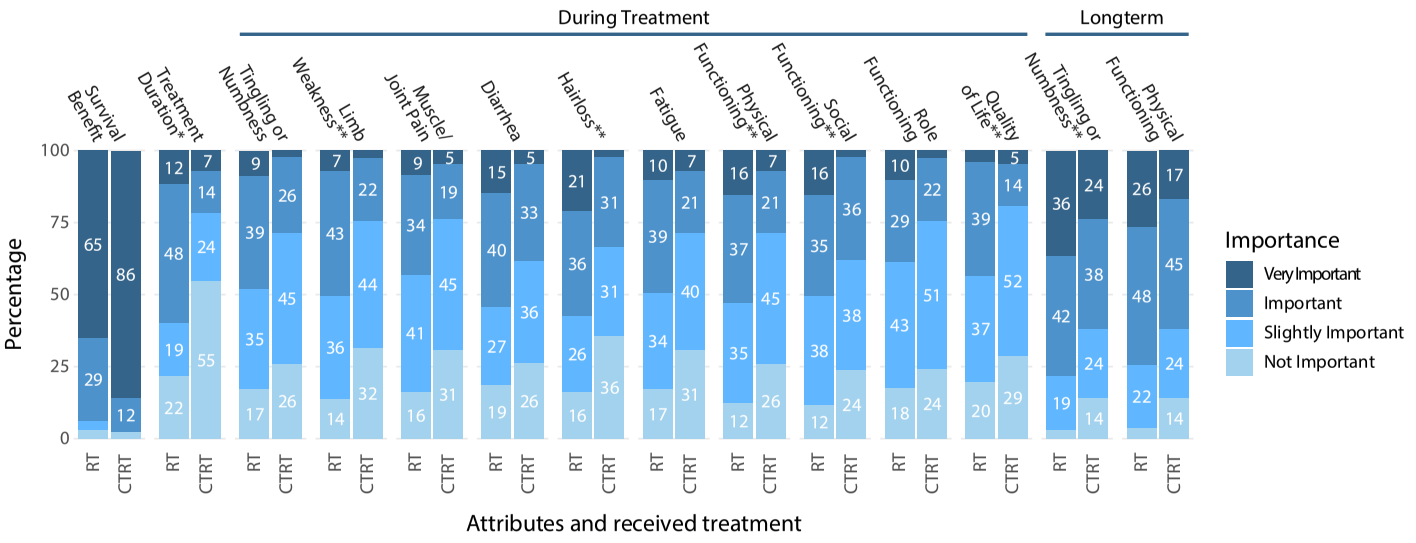


Figure B1. Attribute importance of patients who received adjuvant radiotherapy alone versus patients who received chemoradiotherapy.
CTRT = chemoradiotherapy; RT = radiotherapy.
p values less than or equal to 0.01 show significance; ***p* values less than or equal to 0.05 show a trend.

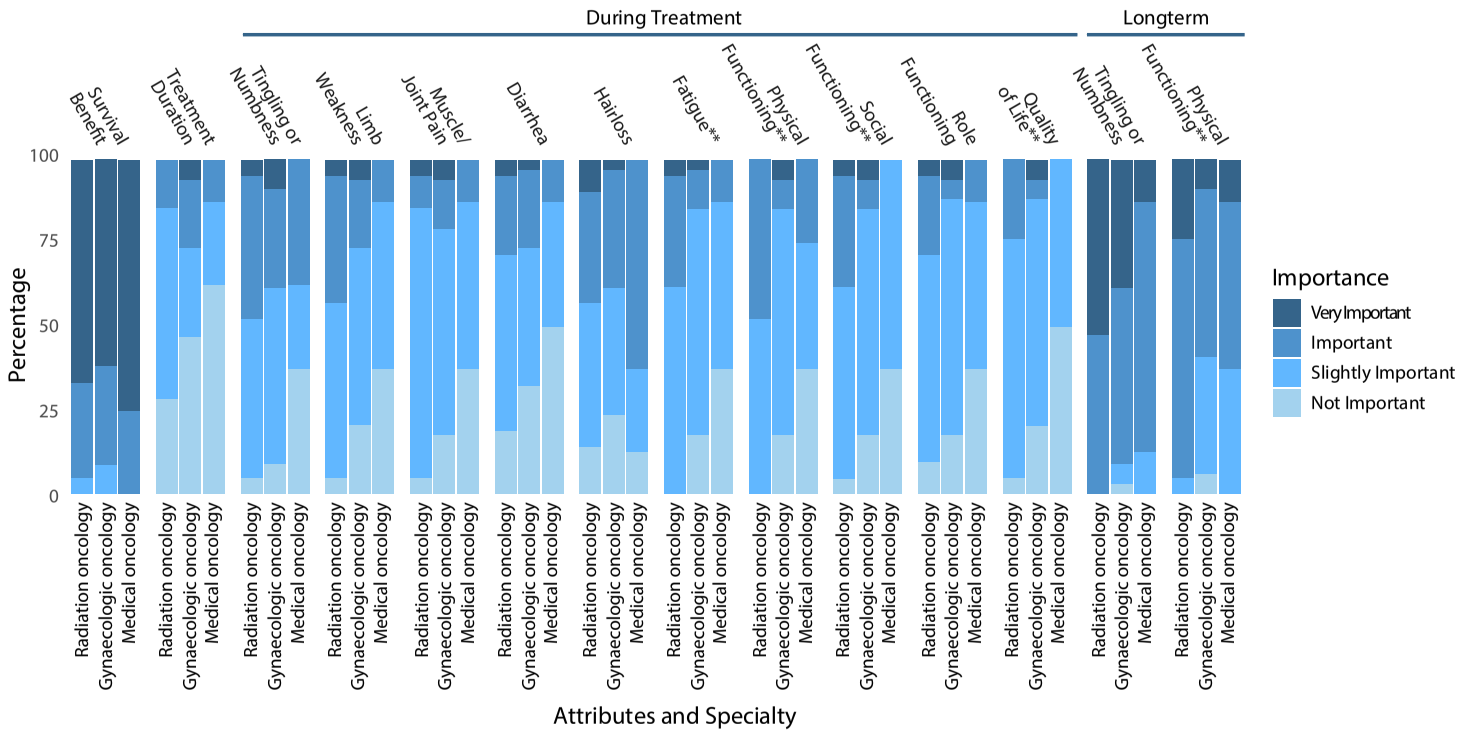


Figure B2. Attribute importance of clinicians according to their specialty: Radiation oncology, gynaecologic oncology versus medical oncology.
p values less than or equal to 0.01 were deemed significant; **p values less than or equal to 0.05 show a trend.

Chapter 4

Prevalence and prognosis of Lynch syndrome and sporadic mismatch repair deficiency in endometrial cancer

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Journal of the National Cancer Institute 2021; 113(9):1212-1220

ABSTRACT

Background

Standard screening of endometrial cancer (EC) for Lynch syndrome (LS) is gaining traction; however, the prognostic impact of an underlying hereditary etiology is unknown. We established the prevalence, prognosis, and subsequent primary cancer incidence of patients with LS-associated EC in relation to sporadic mismatch repair deficient (MMRd)-EC in the large combined Post Operative Radiation Therapy in Endometrial Carcinoma-1, -2, and -3 trial cohort.

Methods

After MMR-immunohistochemistry, *MLH1* promoter methylation testing, and next-generation sequencing, tumors were classified into 3 groups according to the molecular cause of their MMRd-EC. Kaplan-Meier method, log-rank test, and Cox model were used for survival analysis. Competing risk analysis was used to estimate the subsequent cancer probability. All statistical tests were 2-sided.

Results

Among the 1336 ECs, 410 (30.7%) were MMRd. A total of 380 (92.7%) were fully triaged: 275 (72.4%) were *MLH1* hypermethylated MMRd-ECs; 36 (9.5%) LS MMRd-ECs, and 69 (18.2%) MMRd-ECs due to other causes. Limiting screening of EC patients to 60 years or younger or to 70 years or younger would have resulted in missing 18 (50.0%) and 6 (16.7%) LS diagnoses, respectively. Five-year recurrence-free survival was 91.7% (95% confidence interval [CI] 83.1% to 100%; hazard ratio 0.45, 95% CI 0.16 to 1.24; $p = .12$) for LS, 95.5% (95% CI 90.7% to 100%; hazard ratio = 0.17, 95% CI 0.05 to 0.55; $p = .003$) for "other" vs 78.6% (95% CI 73.8% to 83.7%) for *MLH1* hypermethylated MMRd-EC. The probability of subsequent LS-associated cancer at 10 years was 11.6% (95% CI 0.0% to 24.7%), 1.5% (95% CI 0.0% to 4.3%), and 7.0% (95% CI 3.0% to 10.9%) within the LS, "other," and *MLH1* hypermethylated MMRd-EC groups, respectively.

Conclusions

The LS prevalence in the Post Operative Radiation Therapy in Endometrial Carcinoma trial population was 2.8% and among MMRd-ECs was 9.5%. Patients with LS-associated ECs showed a trend towards better recurrence-free survival and higher risk for second cancers compared with patients with *MLH1* hypermethylated MMRd-EC.

Introduction

The diagnosis of Lynch syndrome (LS) in endometrial cancer (EC) is crucial for counseling and cancer surveillance of patients and their relatives. LS is a highly penetrant, hereditary, cancer-prone syndrome caused by germline variants in the DNA mismatch repair (MMR) genes: mutL homologue 1 (*MLH1*), mutS homologue 2 (*MSH2*), mutS homologue 6 (*MSH6*), or postmeiotic segregation increased 2 (*PMS2*). The cancer risk varies per gene and is substantially lower for *PMS2*.[1, 2] EC is often the first malignancy affecting women with LS,[3] and their risk of metachronous cancer is approximately 24% at 10 years.[4]

LS-associated cancers arise following MMR deficiency (MMRd) due to the somatic inactivation of the remaining wild-type MMR allele. MMRd leads to the accumulation of mismatches, insertions, and deletions in repeated sequences also known as microsatellite instability (MSI). MMRd is not an exclusive feature of LS; the vast majority (about 70%) of MMRd-ECs present with somatic inactivation of the *MLH1* gene via hypermethylation of the promoter region.[5, 6] Most of the cases that are neither *MLH1* hypermethylated nor harbor a MMR germline variant are considered sporadic due to biallelic somatic *MMR* gene inactivation; few are caused by an undetectable hereditary syndrome (frequently referred to as Lynch-like syndrome).[7-9] MMRd-ECs are known to have an intermediate prognosis within the molecular classification with a good response to immunotherapy.[10-13] The diagnosis of LS may allow clinicians to tailor treatment and patient information; LS-associated tumors may have a more favorable outcome,[14] although there are no previous studies available on the prognostic impact of LS among MMRd-ECs.

Tumor triage by MMR-immunohistochemistry (IHC) and/or MSI analysis in combination with targeted *MLH1* methylation testing can identify patients with LS. The Proportion of Endometrial Tumours Associated Lynch Syndrome (PETALS) study showed that IHC-based triage is most accurate, whereas clinical selection based on age and family history were imprecise predictors.[15] Overall, an estimated 3% of EC cases are associated with LS,[15-17] which is similar in colorectal cancer (CRC).[18] However, these estimations were mostly based on small trials with methodological heterogeneity, often selecting their test population by age and/or family history, and incomplete testing.[16]

Given its relative rarity, the prevalence and prognosis of LS should be investigated in a large population, such as the well-documented combined cohort of the Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1, -2, and -3 trials. These randomized controlled trials have had a major impact on guidelines for treatment in ECs.[19-21] Together they included 1336 evaluable patients comprising all risk groups with long and complete follow-up information and collected tumor blocks. The aim of our

study was to investigate the prevalence and prognosis of LS-associated EC in relation to *MLH1* hypermethylated MMRd-EC. Secondary objectives were to evaluate currently used age criteria for IHC-based tumor triage and the probability of developing a subsequent primary LS-associated cancer.

Methods

Study population

In total, 1336 of 1801 ECs from the PORTEC-1, -2, and -3 clinical trials were eligible for analysis based on availability of formalin-fixed paraffin-embedded (FFPE) slides. In the PORTEC-1 trial (1990-1997), 714 patients with stage I low-intermediate and high-intermediate risk EC were randomly assigned to receive pelvic radiotherapy or no additional treatment.[19] In the PORTEC-2 trial (2002-2006), 427 endometrioid EC patients with high-intermediate risk features were randomly assigned to receive pelvic radiotherapy or vaginal brachytherapy (if stage I: ≥60 years).[20] In the international PORTEC-3 trial (2006-2013), 660 EC patients with high-risk features were randomly assigned to receive pelvic radiotherapy or chemoradiotherapy.[21] In all trials, patients with a history of invasive cancer (for PORTEC-3 within the last 10 years), except for nonmelanoma skin cancer, were excluded. Full details and results of these trials have been published previously.[19-21] The study protocols were approved by the Dutch Cancer Society and the medical ethics committees at participating centers. All patients provided informed consent for participation in the trial, and for use of their tumor block for subsequent translational research. Clinicopathological data including p53-IHC and *POLE*-mutation status were obtained from the trial databases. Specific ethics approval was obtained for variant analysis on normal tissue among those suspected of LS. Cases from PORTEC-1 and -2 were analyzed anonymized in view of the long interval since recruitment. Cases from PORTEC-3 who were found to have LS were informed by their own physicians if LS had not been already diagnosed clinically. PORTEC-1 was conducted before time of trial registries. PORTEC-2 is registered with ISRCTN number ISRCTN16228756, and ClinicalTrials.gov number NCT00376844. PORTEC-3 is registered with ISRCTN number ISRCTN14387080, and ClinicalTrials.gov number NCT00411138.

IHC, MSI, methylation analysis, and next-generation sequencing

Patients were included in the current analysis if they showed loss of expression of at least 1 of the 4 MMR proteins with positive internal control (including subclonal loss defined as abrupt and complete regional loss with intervening stromal positivity) or MSI-high status when MMR-IHC failed. Details on MMR-IHC and MSI testing and scoring were described previously.[5, 11, 12, 22] Cases with MMRd phenotype are referred to as MMRd-EC in this study irrespective of *POLE* mutation status.

MLH1 methylation testing was performed on MLH1-deficient and/or MSI-high tumors as described previously.[23] All cases with loss of MLH1 or MSI-high status without *MLH1* hypermethylation; loss of MSH2 and/or MSH6; or isolated loss of PMS2 were triaged as potential LS-associated MMRd-EC. DNA isolated from matched normal/tumor FFPE tissues of these cases was amplified using long-range polymerase chain reaction followed by targeted next-NGS for variants in the exonic regions of *MLH1, MSH2, MSH6, PMS2, POLE*, and *POLD1* using the Ion Proton System or Ion S5 System (Thermo Fisher Scientific, MA, USA).[24, 25] Variants were annotated according to the following GenBank reference sequences: NM_000249.3 (*MLH1*), NM_000251.2 (*MSH2*), NM_000179.2 (*MSH6*), NM_000535.5 (*PMS2*), NM_006231.2 (*POLE*), and NM_001256849.1 (*POLD1*). All patients with germline variants (likely) affecting function (*path_MMR*) were verified by a clinical laboratory geneticist (C.M.T.) and considered to have LS.

Statistical analysis

Following complete triage, cases were classified into 3 groups according to the molecular cause of their MMRd-EC: LS, methylated (including cases with *MLH1* hypermethylation and subclonal MLH1 loss), and other causes (a mixed group having alternative causes of MMRd; see the Appendix Methods and Appendix Figure A1 for full definitions). $\chi 2$ Statistics or Fisher's exact test for categorical variables and 1-way analysis of variance or Kruskal-Wallis test for continuous variables were used to compare characteristics. The sample size ensured sufficient power to detect an LS prevalence of 3.0% with a precision of 0.009 (95% confidence interval [CI] 2.1% to 3.9%) within the whole population and a prevalence of 12.0% with a precision of 0.03 (95% CI 9.0% to 15.0%) within the MMRd group.[26] Recurrence-free survival (RFS) was defined as time from random assignment to date of first relapse or death of any cause, whichever occurred first. Overall survival (OS) was defined as time from random assignment to date of death of any cause. Patients without an RFS or OS event were censored at the date of last contact. Five-year survival rates were estimated using the Kaplan-Meier method and compared with log-rank test. Cox proportional hazard models were used to estimate hazard ratios (HRs) over time; for adjusted analysis, age was included as covariate. The proportional hazard assumption was verified using Schoenfeld residuals. A competing-risk model with death as a competing event was used to estimate the cumulative incidence of developing a LS-associated second primary cancer (ie, colorectal, gallbladder, kidney, pancreas, small intestine, stomach, urinary bladder, and ureter cancer) in the different groups. A cause-specific Cox proportional hazard model was used to assess the statistical difference between the estimated probabilities. Time at risk started at random assignment and ended at date of occurrence of the first second cancer, death, or last date of study follow-up. *P* values less than .05 (2-tailed) were considered statistically significant. Statistical analyses were performed using R version 3.6.1.

Results

Study population

Among the 1336 evaluable ECs, 410 (30.7%) were MMRd and eligible for further analysis. Median age of MMRd-EC patients was 65 years (interquartile range = 59-73 years). Most MMRd-ECs were early-stage tumors (74.2%) of low-grade endometrioid subtype (66.8%) and were treated with pelvic radiotherapy (51.7%). All characteristics of MMRd-ECs differed between the 3 PORTEC trials, in line with the inclusion criteria (Table 1).

Table 1. Patient, tumor and treatment characteristics

	All MMRd-EC	**PORTEC 1**	**PORTEC 2**	**PORTEC 3**	***p*-value**
	***n*=410 (100.0)**	***n*=145 (35.6)**	***n*=114 (27.8)**	***n*=151 (36.8)**	
Age at randomization					<0.001
Median (IQR)	65 (59-73)	67 (61-73)	70 (65-77)	60 (56-66)	
FIGO 2009 stage					<0.001
IA	104 (25.4)	62 (42.8)	25 (21.9)	17 (11.3)	
IB	200 (48.8)	83 (57.2)	87 (76.3)	30 (19.9)	
II	36 (8.8)	0 (0.0)	1 (0.9)	35 (23.2)	
III	70 (17.1)	0 (0.0)	1 (0.9)	69 (45.7)	
Histological grade and type					<0.001
EEC grade 1/2	274 (66.8)	122 (84.1)	91 (79.8)	61 (40.4)	
EEC grade 3	99 (24.1)	22 (15.2)	21 (18.4)	56 (37.1)	
Serous	11 (2.7)	1 (0.7)	2 (1.8)	8 (5.3)	
Clear Cell	12 (2.9)	0 (0.0)	0 (0.0)	12 (7.9)	
Other	14 (3.4)	0 (0.0)	0 (0.0)	14 (9.3)	
Myometrial invasion					0.001
≥50%	274 (66.8)	83 (57.2)	90 (78.9)	101 (66.9)	
LVSI					<0.001
Present	131 (32.0)	13 (9.0)	16 (14.0)	102 (67.5)	
Received adjuvant treatment					<0.001
No treatment	73 (17.8)	71 (49.0)	2 (1.8)	0 (0.0)	
EBRT	212 (51.7)	74 (51.0)	58 (50.9)	80 (53.0)	
VBT	54 (13.2)	0 (0.0)	54 (47.4)	0 (0.0)	
CTRT	71 (17.3)	0 (0.0)	0 (0.0)	71 (47.0)	

NOTE. Data reported as No. (%) unless otherwise indicated.

CTRT = combined adjuvant chemotherapy and radiotherapy; EBRT = external beam radiotherapy; EC = endometrial cancer; EEC = endometrioid endometrial cancer; FIGO = International Federation of Gynecology and Obstetrics; LVSI = lymphovascular space invasion; MMRd = mismatch repair deficient; PORTEC = Post Operative Radiation Therapy in Endometrial Carcinoma; VBT = vaginal brachytherapy.

MMR causes and variant analysis

Complete triage was accomplished for 380 (92.7%) of the MMRd-ECs (Figure 1; insufficient material in 27 cases for *MLH1* methylation assay and 3 for NGS). Thirty-six *path_MMR* variant carriers were identified, giving a 2.8% LS prevalence in the overall population and a 9.5% LS prevalence within the MMRd group. There were 18 *path_MSH6*, 10 *path_PMS2*, 6 *path_MSH2*, and 2 *path_MLH1* variant carriers. An overview of the LS cases is displayed in Table 2. In total, 275 (72.4%) cases were classified as methylated. The remaining 69 (18.2%) MMRd cases were neither LS nor *MLH1* hypermethylated and were therefore classified as "other."

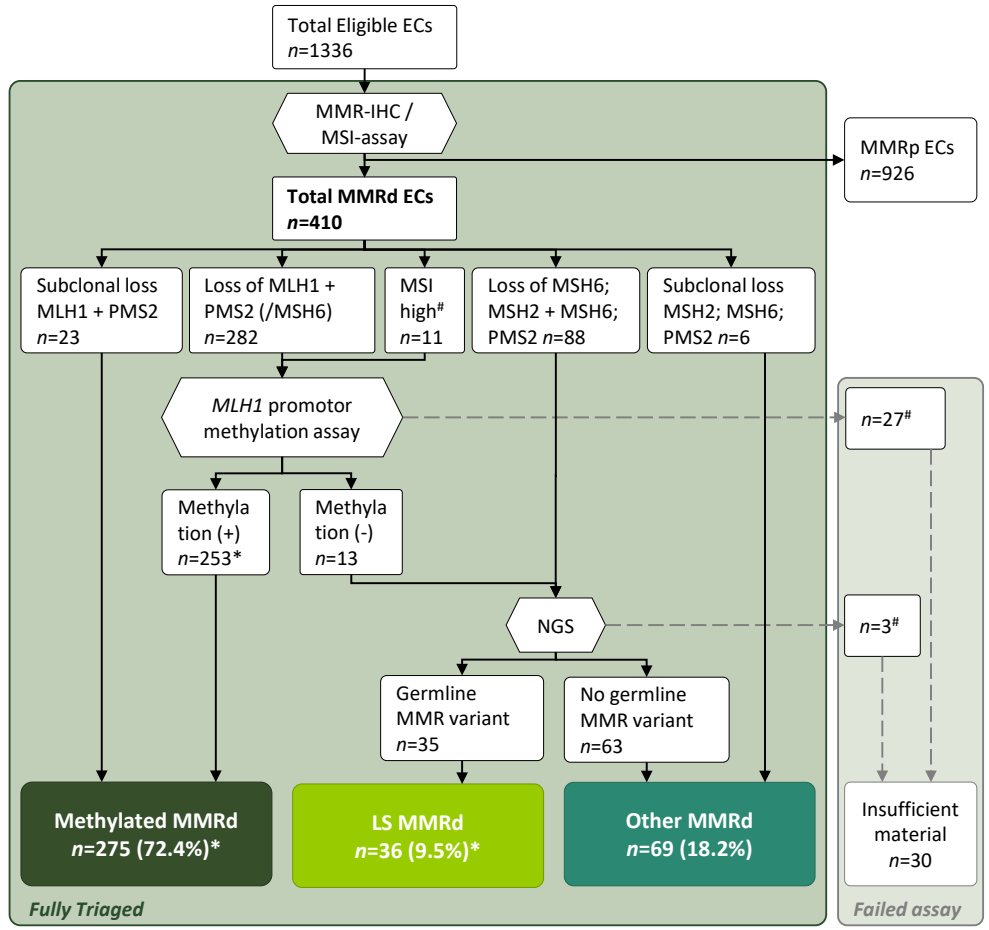

Figure 1. Flowchart

*One case with *MLH1* promoter hypermethylation in the tumor carried a germline *MLH1* variant. # Insufficient material for assay; EC = endometrial cancer; LS = Lynch syndrome; Methylation (+) = *MLH1* promoter hypermethylation; Methylation (-) = no *MLH1* promoter hypermethylation; MMR = mismatch repair; MMRd = mismatch repair deficient; MMRp = mismatch repair proficient; MSI = microsatellite instability; NGS = next-generation sequencing.

Table 2. Patient and tumor characteristics of proven LS-associated endometrial cancers

No.	Study	Age	FIGO 2009	Histotype	Grade	Molecular Class by TCGA surrogate	Affected MMR proteins	*MLH1* promoter methylation	Germline	Variant		Class
1	PORTEC-1	47	IB	Endometrioid	G2	MMRd	MSH2 + MSH6	NA	MSH2	c.1351C>T	p.(Gln451*)	5
2	PORTEC-1	67	IB	Endometrioid	G1	MMRd	MSH2 + MSH6	NA	MSH2	c.363T>G	p.(Tyr121*)	5
3	PORTEC-1	52	IA	Endometrioid	G3	MMRd	MSH2 + MSH6	NA	MSH2	c.646-2A>G	p.(?)	4
4	PORTEC-1	54	IA	Endometrioid	G1	MMRd	MSH2 + MSH6	NA	MSH2	c.2458+1G>A	p.(?)	4
5	PORTEC-3	48	IIIC	Endometrioid	G2	MMRd	MSH2 + MSH6	NA	MSH2	c.1285C>T	p.(Gln429*)	5
6	PORTEC-3	37	IIIC	Clear cell	G2	MMRd	MSH2 + MSH6	NA	MSH2[a]	NA	NA	5
7	PORTEC-3	59	IA	Clear cell	G3	MMRd	MSH2 + MSH6	NA	MSH6	c.3188T>G	p.(leu1063Arg)	5
8	PORTEC-1	56	IA	Serous	G3	MMRd-p53abn	MSH2 subclonal + MSH6	NA	MSH6	c.1784delT	p.(Leu595Tyrfs*15)	5
9	PORTEC-1	67	IB	Endometrioid	G1	MMRd	MSH6	NA	MSH6	c.1189_1190insTT	p.(Tyr397Phefs*15)	5
10	PORTEC-1	58	IA	Endometrioid	G1	MMRd	MSH6	NA	MSH6	c.642C>A	p.(Tyr214*)	5
11	PORTEC-2	67	IB	Endometrioid	G1	MMRd	MSH6	NA	MSH6	c.2764C>T	p.(Arg922*)	5
12	PORTEC-2	66	IB	Endometrioid	G3	MMRd	MSH6	NA	MSH6	c.1483C>T	p.(Arg495*)	5
13	PORTEC-2	73	IB	Endometrioid	G1	MMRd-p53abn	MSH6	NA	MSH6	c.1628_1629delAA	p.(Lys543Argfs*19)	5
14	PORTEC-2	82	IIIA	Endometrioid	G1	MMRd	MSH6	NA	MSH6	c.3729_3732dupATTA	p.(Phe1245Ilefs*31)	5
15	PORTEC-2	71	IB	Endometrioid	G2	MMRd-p53abn	MSH6	NA	MSH6	c.2719_2720delGT	p.(Val907Argfs*10)	5
16	PORTEC-3	51	IIIA	Endometrioid	G1	MMRd	MSH6	NA	MSH6	c.3477C>A	p.(Tyr1159*)	5
17	PORTEC-3	55	IIIC	Endometrioid	G3	MMRd-p53abn	MSH6	NA	MSH6	c.2906_2907delAT	p.(Tyr969Leufs*5)	5
18	PORTEC-3	61	IB	Clear cell	G3	MMRd	MSH6	NA	MSH6	c.3838C>T	p.(Gln1280*)	5
19	PORTEC-3	68	IIIA	Endometrioid	G1	MMRd	MSH6	NA	MSH6	c.467C>G	p.(Ser156*)	5
20	PORTEC-3	59	IB	Serous	G3	MMRd-p53abn	MSH6	NA	MSH6	c.3527_3549delGACTTG GTGCCTCAGACAGAATA	p.(Arg1176Asnfs*4)	5
21	PORTEC-3	60	IA	Serous	G3	*POLE*mut-MMRd	MSH6	NA	MSH6	c.2342dupC	p.(Leu782Thrfs*3)	5
22	PORTEC-3	59	IB	Clear cell	G3	MMRd	MSH6	NA	MSH6	c.3863_3865dupAAT	p.(Phe1289*)	5
23	PORTEC-3	76	IB	Serous	G3	MMRd	MSH6	NA	MSH6	c.3847_3850dupATTA	p.(Thr1284Asnfs*6)	5
24	PORTEC-3	74	IA	Serous	G3	MMRd-p53abn	MSH6	NA	MSH6	c.10C>T	p.(Gln4*)	4
25	PORTEC-1	57	IB	Endometrioid	G3	MMRd	PMS2	NA	PMS2	c.1882C>T	p.(Arg628*)	5
26	PORTEC-1	66	IB	Endometrioid	G1	MMRd	PMS2	NA	PMS2	c.1882C>T	p.(Arg628*)	5
27	PORTEC-1	64	IB	Endometrioid	G3	MMRd-p53abn	PMS2	NA	PMS2	c.247_250dupTTAA	p.(Thr84Ilefs*9)	5
28	PORTEC-1	65	IB	Endometrioid	G1	MMRd	PMS2	NA	PMS2	c.1261C>T	p.(Arg421*)	5
29	PORTEC-2	61	IB	Endometrioid	G1	MMRd	PMS2	NA	PMS2	c.904_911delGTCTGCAG	p.(Val302Thrfs*4)	5
30	PORTEC-2	61	IB	Endometrioid	G3	MMRd	PMS2	NA	PMS2	c.1831dupA	p.(Ile611Asnfs*2)	5
31	PORTEC-2	78	IB	Endometrioid	G1	*POLE*mut-MMRd	PMS2	NA	PMS2	c.1882C>T	p.(Arg628*)	5
32	PORTEC-2	62	IB	Endometrioid	G2	MMRd	PMS2	NA	PMS2	c.904_911delGTCTGCAG	p.(Val302Thrfs*4)	5
33	PORTEC-3	54	IB	Endometrioid	G3	MMRd	PMS2	NA	PMS2	c.137G>T	p.(Ser46Ile)	5
34	PORTEC-3	48	II	Endometrioid	G3	MMRd	PMS2	NA	PMS2	c.989-2A>G	p.(Glu330_Glu381del)	4

Table 2. Patient and tumor characteristics of proven LS-associated endometrial cancers *(continued)*

No.	Study	Age	FIGO 2009	Histotype	Grade	Molecular Class by TCGA surrogate	Affected MMR proteins
35	PORTEC-3	52	IIIC	Endometrioid	G2	Not classified	MLH1 + PMS2
36	PORTEC-1	48	IB	Endometrioid	G1	MMRd	MSI-high[b]

NOTE. Classification according to the 5-tiered InSiGHT rules: class 5 is pathogenic and class 4 is likely pathogenic.
[a]Loss-of-function variant in *MSH2* gene identified by genetic testing (clinical data) but insufficient material for normal tissue next-generation sequencing.
[b]No material for MLH1 and PMS2 IHC
G = grade; NA = not available; MMRd = mismatch repair deficient; p53abn = p53 abnormal; *POLE*mut = *POLE*-ultramutated; PORTEC = Post Operative Radiation Therapy in Endometrial Carcinoma; TCGA = The Cancer Genome Atlas.

LS patients were younger, with a median age of 60 years (interquartile range = 54-67 years) and more often had p53 aberrant staining (20.0%) and serous (13.9%) or clear cell (8.3%) histology compared with the patients with methylated MMRd-EC (Table 3). Limiting screening of EC patients to age 50 years or younger, 60 years or younger, and 70 years or younger would have missed 31 (86.1%), 18 (50.0%), and 6 (16.7%) LS diagnoses, respectively. Figure 2 displays the distribution of the involved MMR proteins; all LS cases identified by the 4-panel approach would also have been identified by a 2-panel approach including only PMS2- and MSH6-IHC. No germline *POLE/POLD1* variants affecting function were identified. LS patients with *path_MSH6* and *path_PMS2* variants were older than those with *path_MLH1* and *path_MSH2* variants (median age = 63, 62, 50, and 50 years, respectively; $p = .01$; Appendix Table A1).

Survival

The estimated RFS for the MMRd population at 5 years was 83.7% (95% CI 80.1% to 87.4%): 91.7% (95% CI 83.1% to 100%) for patients with LS-associated MMRd-EC, 78.6% (95% CI 73.8% to 83.7%) for patients with methylated MMRd-EC, and 95.5% (95% CI 90.7% to 100%) for patients with other causes of MMRd-EC ($p = .001$; Figure 3A; LS vs methylated: HR 0.45, 95% CI 0.16 to 1.24, $p = .12$; other vs methylated: HR 0.17, 95% CI 0.05 to 0.55, $p = .003$).

MLH1 promoter methylation	Germline Variant			Class
Methylated	MLH1	c.794G>C	p.(Arg265Pro)	4
Unmethylated	MLH1	c.806C>G	p.(Ser269*)	5

MMR protein expression				All MMRd-EC		Triaged MMRd-EC		
						Methylated	Other	LS
MLH1	PMS2[a]	MSH6[a]	MSH2	No.[b]	%	No.	No.	No.
R	R	CL	R	32	8%	0	16	16
R	CL	R	R	15	4%	0	5	10
R	R	CL	CL	33	8%	0	25	7
R	R	CL	SL	3	1%	0	1	1
CL	CL	R	R	254	62%	226	8	1
SL	CL	R	R	6	2%	5	1	0
CL	CL	SL	R	11	3%	9	1	0
UK	CL	R	R	5	1%	2	0	0
CL	R	R	R	4	1%	1	0	0
CL	SL	R	R	1	0%	1	0	0
CL	CL	CL	R	1	0%	1	0	0
SL	SL	CL	CL	2	1%	0	2	0
R	R	R	CL	1	0%	0	1	0
SL	CL	SL	R	1	0%	0	1	0
R	CL	CL	CL	1	0%	0	0	0
SL	SL	R	R	22	5%	22	0	0
R	R	SL	SL	4	1%	0	4	0
R	SL	R	R	1	0%	0	1	0
R	R	R	SL	1	0%	0	1	0
SL	R	R	R	1	0%	1	0	0
UK	UK	UK	UK	11	3%	7	2	1

CL Complete loss SL Subclonal loss R Retained UK Unknown

Figure 2. Details on the mismatch repair (MMR) protein expression according to the molecular cause of their MMR-deficient endometrial cancer (MMRd-EC).
MMR protein expression was scored as following: complete loss (CL), retained (R), subclonal loss (SL), unknown/failed (UK). [a]The concordance of these 2 columns shows that a 2-antibody (MSH6 and PMS2) panel is as sensitive as the full panel to detect Lynch syndrome (LS). [b]All MMRd-ECs including those with insufficient material for *MLH1* methylation assay (n = 27) and next-generation sequencing ($n = 3$).

The estimated OS for the MMRd population at 5 years was 82.8% (95% CI 79.2% to 86.5%): 88.5% (95% CI 78.5% to 99.8%) for patients with LS-associated MMRd-EC, 78.5% (95% CI 73.7% to 83.5%) for patients with methylated MMRd-EC, and 97.0% (95% CI 93.0% to 100%) for patients with other causes of MMRd-EC ($p < .001$; Figure 3B; LS vs methylated: HR 0.50, 95% CI 0.24 to 1.02, $p = .06$; other vs methylated: HR 0.27, 95% CI 0.13 to 0.55, $p < .001$). After adjustment for age, the trend for better OS in the LS group was no longer observed (vs methylated MMRd-EC: HR 0.73, 95% CI 0.35 to 1.52, $p = .40$), whereas age and having another cause of MMRd were statistically significant prognostic factors (HR 1.07, 95% CI 1.04 to 1.09, $p < .001$; other vs methylated MMRd-EC: HR 0.41, 95% CI 0.20 to 0.85, $p = .02$).

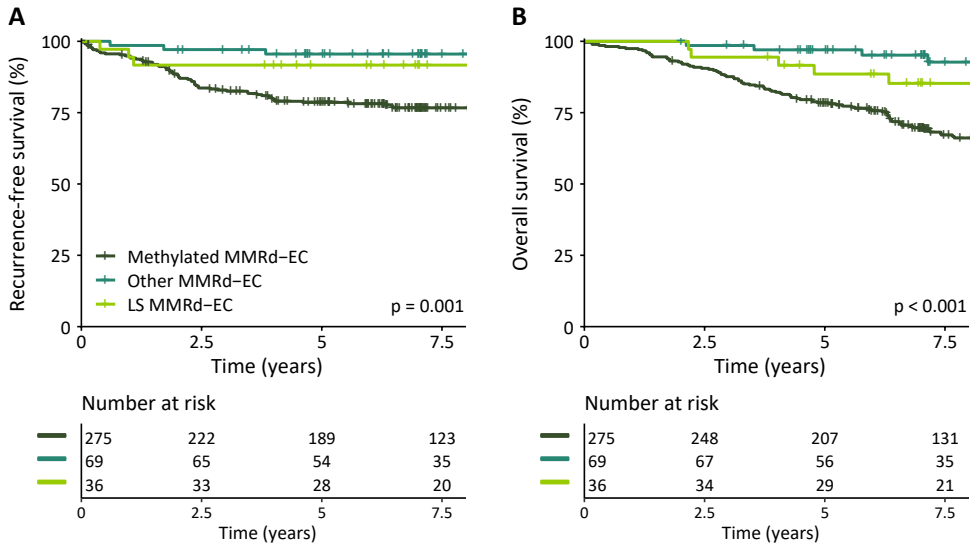

Figure 3. Kaplan-Meier survival curves for recurrence-free survival (A) and overall survival (B) for patients with methylated mismatch repair deficient (MMRd), other MMRd and Lynch syndrome (LS) associated MMRd endometrial cancer (EC) including cases with a concurrent *POLE* variant affecting function (*POLE*mut-MMRd-EC). *P* values reflect 2-sided log-rank test.

Second primary cancers

At 10 years, the cumulative incidence of developing a second LS-associated tumor was 11.6% (95% CI 0.0% to 24.7%) among EC patients with LS, 1.5% (95% CI 0.0% to 4.3%) among patients with other MMRd-EC, and 7.0% (95% CI 3.0% to 10.9%) among patients with methylated MMRd-EC (Appendix Figure A2). Three of the 4 LS-patients who developed a second primary LS-associated cancer had colon cancer (after 3.8, 4.8, and 14.9 years) and 1 had ureteral cancer (after 8.0 years; Appendix Table A2, shows cancer type distribution). The cause-specific hazard ratio for developing an LS-associated second cancer was 1.9 (95% CI 0.63 to 5.7; $p = .26$) for patients with LS vs patients with methylated MMRd-EC.

Table 3. Characteristics according to the molecular cause of their MMRd-EC.

	All MMRd-EC	**Methylated**	**Other**	**LS**	***p*-value**
	n*=410	***n*=275 (72.4)**	***n*=69 (18.2)**	***n*=36 (9.5)**	
Age at randomization					<0.001
Median (IQR)	65 (59-73)	67 (62-74)	59 (55-66)	60 (54-67)	
Trial					0.002
PORTEC-1	145 (35.4)	99 (36.0)	22 (31.9)	12 (33.3)	
PORTEC-2	114 (27.8)	87 (31.6)	8 (11.6)	9 (25.0)	
PORTEC-3	151 (36.8)	89 (32.4)	39 (56.5)	15 (41.7)	
FIGO 2009 stage					0.199
IA	104 (25.4)	70 (25.5)	17 (24.6)	7 (19.4)	
IB	200 (48.8)	137 (49.8)	27 (39.1)	21 (58.3)	
II	36 (8.8)	22 (8.0)	11 (15.9)	1 (2.8)	
III	70 (17.1)	46 (16.7)	14 (20.3)	7 (19.4)	
Histological grade and type					<0.001
EEC grade 1/2	274 (66.8)	197 (71.6)	40 (58.0)	19 (52.8)	
EEC grade 3	99 (24.1)	64 (23.3)	18 (26.1)	8 (22.2)	
Serous	11 (2.7)	2 (0.7)	4 (5.8)	5 (13.9)	
Clear Cell	12 (2.9)	2 (0.7)	6 (8.7)	3 (8.3)	
Other	14 (3.4)	10 (3.6)	1 (1.4)	1 (2.8)	
Myometrial invasion					0.407
>50%	274 (66.8)	187 (68.0)	43 (62.3)	27 (75.0)	
LVSI					0.957
Present	131 (32.0)	90 (32.7)	23 (33.3)	11 (30.6)	
***POLE*mut in tumour**					0.002
EDM	19 (4.7)	8 (2.9)	9 (13.4)	2 (5.7)	
p53 IHC					<0.001
Aberrant	31 (7.7)	7 (2.6)	14 (20.9)	7 (20.0)	
Received adjuvant treatment					0.104
No treatment	73 (17.8)	47 (17.1)	10 (14.5)	9 (25.0)	
EBRT	212 (51.7)	145 (52.7)	40 (58.0)	13 (36.1)	
VBT	54 (13.2)	39 (14.2)	3 (4.3)	6 (16.7)	
CTRT	71 (17.3)	44 (16.0)	16 (23.2)	8 (22.2)	

NOTE. Data reported as No. (%) unless otherwise indicated.

CTRT = combined adjuvant chemotherapy and radiotherapy; EBRT = external beam radiotherapy; EC = endometrial cancer; EDM = exonuclease domain mutations; EEC = endometrioid endometrial cancer; FIGO = International Federation of Gynecology and Obstetrics; IHC = immunohistochemistry; LS = Lynch syndrome; LVSI = lymphovascular space invasion; MMRd = mismatch repair deficient; *POLE*mut = *POLE*-ultramutated; PORTEC = Post Operative Radiation Therapy in Endometrial Carcinoma; VBT = vaginal brachytherapy.

*All MMRd-ECs including those with insufficient material for *MLH1* methylation assay ($n = 27$) and normal tissue NGS ($n = 3$).

Discussion

After complete IHC-based tumor triage, we found a 2.8% prevalence of LS in 1 of the largest EC trial populations worldwide, comprising all risk groups with long and complete follow-up. The prevalence of LS among patients with MMRd-EC was 9.5%. Patients with LS were relatively young, but restricted testing to women who are 60 years or younger would have missed one-half of the cases. Patients with LS tend to have a better RFS and a higher risk of developing second primary cancers compared with patients with methylated MMRd-ECs. No trend for more favorable OS was found after adjustment for age.

This is the first study to our knowledge investigating the prognostic value of LS within the MMRd-EC subgroup. Most of the recent research showed that MMRd-ECs, predominantly driven by the large number of *MLH1* hypermethylated cases, have an intermediate prognosis within the molecular classification introduced by The Cancer Genome Atlas.[10-12] Our survival analysis showed that EC patients with LS tend to have a better RFS than patients with methylated MMRd-EC (HR 0.45; $p = .12$), whereas LS had no statistically significant prognostic value for OS after adjustment for age (age-adjusted HR 0.73; $p = .40$). The favorable prognosis has been assumed to be induced by the active local immune response.[14, 27] Comparable survival analysis in CRC has been published. One study showing a better OS for 85 CRC patients with LS compared with 67 sporadic MMRd patients after adjustment for age, stage, and *BRAF* status (HR 0.29, 95% CI 0.09 to 0.95; $p = .04$).[28] The other study also showing better OS in 37 CRC patients with LS compared with 106 methylated MMRd patients, although the difference was minimal after adjusting for age and stage.[29]

The cumulative incidence for developing a second LS-associated cancer at 10 years was 11.6% (95% CI 0.0% to 24.7%) for patients with LS vs 7.0% (95% CI 3.0% to 10.9%) for patients with methylated MMRd-EC (HR 1.90, 95% CI 0.63 to 5.7; $p = .26$). Our analysis was underpowered due to the small number of events in the LS group. Nevertheless, the elevated risk strengthens previous reports on subsequent cancers in EC or non-CRC LS patients (15%-24%)[4, 30] and is of importance for surveillance strategies.

The 2.8% prevalence of LS-EC is consistent with previous publications in which prevalences of 2.8% to 3.2% were reported.[15-17] This prevalence is likely a slight underestimation. Firstly, our NGS panel did not include EPCAM and could not detect large rearrangements. To detect large rearrangement in EPCAM or the MMR genes, Multiplex Ligation-dependent Probe Amplification is most commonly used but performs poorly on FFPE tissue. Secondly, the patient selection in our trial design may have affected the prevalence. Patients younger than 60 years with stage I ECs were excluded from the PORTEC-2 trial. Nevertheless, the total PORTEC population deviates minimally from the general EC population as suggested by the similar age in the PETALS study, an unselected, prospective, cross-sectional study in the United Kingdom among 500 EC patients.[15] Moreover, patients with a history of cancer were excluded from the PORTEC trials. The PORTEC population represents women with EC as their sentinel LS-associated malignancy, which is the case in more than one-half of those women with LS who develop cancer.[3] Although this selection has potentially led to a slight underestimation of the prevalence of LS in EC, it does represent the patients in which LS could be detected by IHC-based tumor triage. The recently published meta-analysis by Ryan et al.[16] included mostly small trials with methodological heterogeneity, often selecting their test population by age and/or family history, and incomplete testing; only 1 publication included over 1000 ECs, but germline testing was limited to the minority of the triaged potential LS cases.[6] Our study is the first with LS testing in an EC population consisting of more than 1000 women with almost complete MMR-IHC, targeted *MLH1* methylation testing, and MMR germline testing, making our estimates more reliable.

The *path_MSH6* carrier rate of 50.0% among the PORTEC patients with LS is consistent with LS testing results in other unselected EC populations,[15, 17] but it is remarkably high compared with LS registry data. Only 13% of *path_MMR* carriers in the clinically selected Prospective Lynch Syndrome Database bear *path_MSH6*.[1] As mentioned above, our cohort represents patients with EC as their sentinel cancer likely to induce a lower frequency of *path_MLH1* and *path_MSH2*. Moreover, it must be considered that most of our participants were Dutch, and the *path_MSH6* rate of 30% among the Dutch LS registry patients was relatively high compared with the overall Prospective Lynch Syndrome Database.[31] Lastly, *path_MSH6* families are not identified efficiently by current clinical criteria for LS[32] due to the later age of onset of CRC, incomplete penetrance, and a higher risk and later age of onset of EC.[1, 33-35] The same applies to *path_PMS2* carriers with a substantially lower cancer risk.[1, 2, 15, 16] Correspondingly, the *path_MSH6* and *path_PMS2* carriers were older than the *path_MLH1* and *path_MSH2* carriers in our population.

Triage of incident ECs based on IHC with targeted *MLH1* methylation testing, as has been adopted widely for CRC, may be a more effective strategy to identify these LS families than age- and family history–based triage. An upper age screening limit would not be recommended, because limiting screening to EC patients who are aged 70 years or younger would have missed 6 (16.7%) LS diagnoses. We confirmed that a 2-antibody panel including MSH6- and PMS2-IHC, with MSH2- or MLH1-IHC only in case of inconclusive staining, is as sensitive as the full panel to detect LS, so this could be a reliable alternative to improve cost-effectiveness.[5, 36]

A limitation of our study was the lack of germline LS sequencing on the whole study population. Therefore, sensitivity of the IHC-based triage to identify LS patients could not be assessed. Some patients with LS might have been diagnosed before entering the trial, although many were diagnosed after inclusion and had no prior knowledge of the germline mutation.

The diagnosis of LS in EC is crucial for counseling and cancer surveillance even though these patients might be older than those presenting with CRC.[18] Moreover, LS screening in incident ECs will have consequences for the patient's family. Cascade testing of at-risk relatives can identify *path_MMR* carriers who can benefit from cancer surveillance and risk-reducing treatment.[37, 38] The clinical impact depends on the gene-specific cancer risk, which is substantially lower for *path_PMS2* carriers.[1, 2] Finally, LS identification may have consequences by allowing clinicians to better estimate and explain prognosis, and to potentially tailor treatment in the upcoming immunotherapy era.[14, 27, 39]

Further research into the causes of the 63 cases with neither *MLH1* hypermethylation nor a *MMR* germline variant is ongoing. It is hypothesized that the majority will be explained by a sporadic origin through biallelic somatic MMR inactivation.[15, 40] The determination of a sporadic explanation excludes potential undetectable LS (or 'Lynch-like' syndrome) and will avoid a clinical management dilemma in those cases.

In conclusion, Lynch syndrome was identified using MMR-IHC with targeted *MLH1* methylation–based triage in 2.8% of 1336 patients with EC from the combined PORTEC-1, -2, and -3 trials, corresponding to 9.5% of the MMRd tumors. LS was mainly caused by germline variants in the *MSH6* and *PMS2* genes. Patients with LS-associated ECs showed a trend towards better RFS and higher risk for second primary cancers compared with patients with ECs caused by *MLH1* hypermethylation. Besides a prognostic impact, screening all incident ECs without an upper age limit to identify LS using tumor-based triage may benefit counseling, affect treatment decisions, and facilitate prevention strategies for current and future patients and their families.

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APPENDIX

Supplementary Methods

Definitions

MMRd-EC = All EC with loss of expression of one or more MMR proteins and positive internal control irrespective of *POLE*- and MSI-status. In case MSI testing was performed, but no MMR-IHC, all EC with MSI-high status. In case not all four MMR proteins could be stained: All EC with loss of expression of at least one MMR protein or MSI-high status.

MMRp-EC = All EC with retained expression of all four MMR proteins. In case MSI testing is performed, but no MMR-IHC, all EC with MSI-low or MSS status.

Suspected of Lynch syndrome/Potential LS-associated MMRd-EC = All MMRd-EC with loss of MLH1 expression without hypermethylation of the *MLH1* promotor; loss of MSH2 and/or MSH6 expression or isolated loss of PMS2 expression. In case MSI testing was performed, but no MMR-IHC, all MMRd-EC with MSI-high status without hypermethylation of the *MLH1* promotor. In case not all four MMR proteins could be stained: MMRd-EC with loss of MSH2, MSH6 and/or PMS2 with retained MLH1 expression, or loss of MLH1 expression or MSI-high if MLH1-IHC is not available without *MLH1* promotor hypermethylation.

LS-associated MMRd-EC = MMRd-EC with a germline variant (likely) affecting function corresponding with MMR protein loss. Class 4 or 5 according to InSiGHT Variant Classification.

MMRd caused by *MLH1* promotor hypermethylation = All MMRd-EC with loss of MLH1 expression and proven *MLH1* promotor hypermethylation by methylation specific PCR. In case MSI testing was performed, but no MMR-IHC, all EC with MSI-high status and proven *MLH1* promotor hypermethylation. In case not all four MMR proteins could be stained: MMRd-EC with loss of PMS2 and/or MLH1 expression and proven *MLH1* promotor hypermethylation. Also including cases with subclonal loss of MLH1 and total loss of PMS2 expression with *MLH1* promotor hypermethylation.

Subclonal loss of MMR expression = Subclonal loss (≥10%) of one or more MMR proteins (NB excluding cases with complete loss of expression of another MMR protein, than the complete loss of another MMR protein is leading in group allocation).

Methylated MMRd-EC = All EC with MMRd caused by *MLH1* promotor hypermethylation and subclonal loss of MLH1 expression.

MMRd-EC with other causes = MMRd-EC with neither a MMR germline variant affecting function in DNA isolated from normal tissue nor promotor hypermethylation of *MLH1* in the tumor. A mixed group having alternative causes of MMRd. It is hypothesised that the majority will be explained by sporadic origin through biallelic somatic MMR inactivation (i.e. variants affecting function or loss of heterozygosity [LOH]), and few cases may have an undetectable hereditary syndrome (frequently referred to as 'Lynch-like syndrome' in literature).

MMRd-EC with unknown *MLH1* methylation status = All MMRd-EC with loss of MLH1 expression and insufficient material for *MLH1* promoter methylation assay.

Complete triage/Fully triaged = All identified MMRd-EC with successful *MLH1* promoter methylation assay and next-generation sequencing when indicated.

Definition		Depending on performed MMR/MSI test(s)			*MLH1* methylation status	NGS
		MMR-IHC + MSI test or only MMR-IHC	**Only MSI-test**	**MMR-IHC of <4 proteins performed + MSI-test**		
MMRd		Loss of ≥1 MMR proteins	MSI-high	Loss of ≥1 MMR proteins or MSI high		
MMRp		All retained expression	MSI low or MSS	all IHC retained expression + MSI low or MSS		
Suspected of LS / Potential LS-associated		MSH2 and/or MSH6 loss, PMS2 loss		MSH2, MSH6 or PMS2 loss with retained MLH1		
		MLH1 loss	MSI-high	MLH1 loss or MSI-high if MLH1-IHC N/A	Unmethylated	
Methylated MMRd-EC	1	MLH1 loss	MSI-high	PMS2 and/or MLH1 loss or MSI-high if MLH1-IHC N/A	Hypermethylated	
Included subgroups: 1. *MLH1* methylated; 2. Subclonal MLH1 loss;	2	Subclonal MLH1 loss[a]				
LS-associated EC		Suspected of LS; Corresponding to NGS		Suspected of LS; Corresponding to NGS		Pathogenic mutation in normal (and tumor) tissue
MMRd-EC with other cause		Suspected of LS or Subclonal MSH2, MSH6 or PMS2 loss[a]	Suspected of LS	Suspected of LS		1. Double somatic mutations in tumor without pathogenic mutation in normal tissue (Ongoing research)
Included subgroups: 1. Explained somatic 2 (a/b). Unexplained						2a. No pathogenic mutation in normal tissue found and no double somatic alteration in tumor (Ongoing research)
						2b. No pathogenic mutation in normal tissue found and tumor NGS failed
Failed cases	1	MLH1 loss		PMS2 and/or MLH1 loss	Failed	
Included subgroups: 1. Unknown *MLH1* methylation status	2	Suspected of LS	Suspected of LS	Suspected of LS		Normal tissue NGS failed
2. Suspected of LS but failed NGS						

Figure A1. Definitions

Definition depend on the combination of the results of the MMR/MSI test (choose one of the three green columns based on the available test results; MMR-IHC [dark green column] is preferable when available), *MLH1* methylation status (blue) and NGS (orange) in the corresponding row.

[a] NB excluding cases with complete loss of another MMR protein; the complete loss of another MMR protein is leading in group allocation.

EC = endometrial cancer; IHC = immunhistochemistry; LS = Lynch syndrome; MMRd = mismatch repair deficient; MMRp = mismatch repair proficient; MSI = microsatellite instability; N/A = not available; NGS = next-generation sequencing

Table A1. Patient, tumor and treatment characteristics of patients with proven MMR germline variant according to affected gene

	MLH1	PMS2	MSH2	MSH6	*p*-value
	***n*=2**	***n*=10**	***n*=6**	***n*=18**	
Age at randomization					0.011
Median (IQR), y	50 (49-51)	62 (58-65)	50 (47-54)	63 (59-70)	
Trial					0.182
PORTEC-1	1 (50.0)	4 (40.0)	4 (66.7)	3 (16.7)	
PORTEC-2	0 (0.0)	4 (40.0)	0 (0.0)	5 (27.8)	
PORTEC-3	1 (50.0)	2 (20.0)	2 (33.3)	10 (55.6)	
FIGO 2009 stage					0.195
IA	0 (0.0)	0 (0.0)	2 (33.3)	5 (27.8)	
IB	1 (50.0)	9 (90.0)	2 (33.3)	9 (50.0)	
II	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	
III	1 (50.0)	0 (0.0)	2 (33.3)	4 (22.2)	
Histological grade and type					0.302
EEC grade 1/2	2 (100.0)	5 (50.0)	4 (66.7)	8 (44.4)	
EEC grade 3	0 (0.0)	5 (50.0)	1 (16.7)	2 (11.1)	
Serous	0 (0.0)	0 (0.0)	0 (0.0)	5 (27.8)	
Clear cell	0 (0.0)	0 (0.0)	1 (16.7)	2 (11.1)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	
Myometrial invasion					0.18
>50%	1 (50.0)	10 (100.0)	4 (66.7)	12 (66.7)	
LVSI					0.569
Present	0 (0.0)	2 (20.0)	2 (33.3)	7 (38.9)	
***POLE*mut in tumour**					0.858
EDM	0 (0.0)	1 (10.0)	0 (0.0)	1 (5.6)	
p53 IHC					0.224
Aberrant	0 (0.0)	1 (10.0)	0 (0.0)	6 (33.3)	
Received Adjuvant Treatment					0.127
No treatment	1 (50.0)	3 (30.0)	4 (66.7)	1 (5.6)	
EBRT	1 (50.0)	4 (40.0)	0 (0.0)	8 (44.4)	
VBT	0 (0.0)	1 (10.0)	0 (0.0)	5 (27.8)	
CTRT	0 (0.0)	2 (20.0)	2 (33.3)	4 (22.2)	

NOTE. Data reported as No. (%) unless otherwise indicated.

CTRT = combined adjuvant chemotherapy and radiotherapy; EBRT = external beam radiotherapy; EC = endometrial cancer; EDM = exonuclease domain mutations; EEC = endometrioid endometrial cancer; FIGO = International Federation of Gynecology and Obstetrics; LVSI = lymphovascular space invasion; MMRd = mismatch repair; *POLE*mut = *POLE*-ultramutated; PORTEC = Post Operative Radiation Therapy in Endometrial Carcinoma; VBT = vaginal brachytherapy.

Table A2. Distribution of the Lynch syndrome associated second primary cancer types

	Methylated	Other	Lynch
2nd Primary cancers, No. (%)	**15 (5.5)**	**2 (2.9)**	**4 (11.1)**
Type, No. (%)	***N***	***N***	***N***
Colon	5 (33.3)	2 (100)	3 (75.0)
Gallbladder	1 (6.7)	0 (0)	0 (0)
Kidney	1 (6.7)	0 (0)	0 (0)
Pancreas	2 (13.3)	0 (0)	0 (0)
Rectosigmoid	1 (6.7)	0 (0)	0 (0)
Rectum	2 (13.3)	0 (0)	0 (0)
Stomach, excl. cardia	2 (13.3)	0 (0)	0 (0)
Urinary bladder	1 (6.7)	0 (0)	0 (0)
Ureter	0 (0)	0 (0)	1 (25.0)

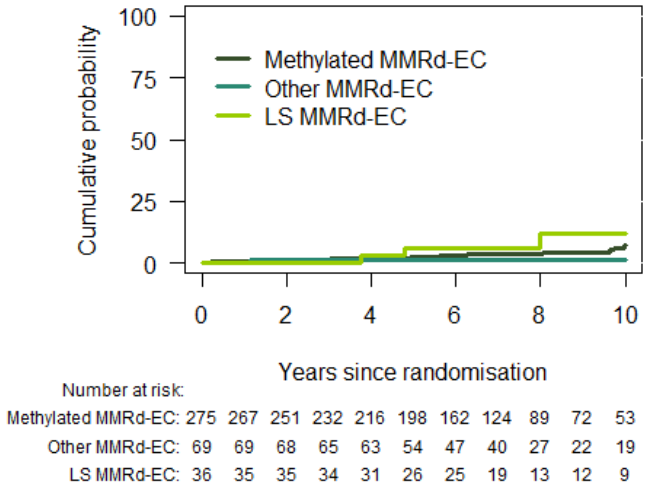

Figure A2. Cumulative incidence of developing a subsequent Lynch syndrome associated primary cancer after a primary endometrial cancer.

Chapter 5

PARP and PD-1/PD-L1 checkpoint inhibition in recurrent or metastatic endometrial cancer

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ABSTRACT

The prognosis of recurrent or metastatic endometrial cancer is poor, with five-year survival of only 10–20%. First-line therapy consists of either platinum-based chemotherapy or hormonal therapy. No standard subsequent-line therapy has been identified. In recent years, significant progress has been made in the knowledge on underlying molecular biology of endometrial cancer and potential targets for therapy have been identified. Targeted therapies as poly (ADP-ribose) polymerase (PARP) inhibitors and immunotherapy as PD-1/PD-L1 checkpoint inhibitors have the potential to be effective against specific subtypes of endometrial cancer. Preclinical studies have shown that combining these agents may result in a synergistic effect. In this review, we focus on the molecular basis of checkpoint inhibition and targeted therapy as PARP inhibition in endometrial cancer and summarize available clinical data, and ongoing and planned clinical trials that investigate these agents as mono- or combination therapies in endometrial cancer and where relevant, other gynecological cancers.

1. Introduction

Endometrial cancer is the most common gynecological cancer in developed countries, and its incidence is gradually rising due to increased obesity and ageing of the population. In contrast to the declining trends for many common cancers, mortality has remained roughly the same for endometrial cancer.[1, 2] Although endometrial cancer is most often diagnosed at an early stage and the prognosis is generally good, a small (but notable) proportion of patients present with or develop metastatic or recurrent disease not amenable to localized therapies; these women have an unfavorable prognosis. First-line therapy for metastatic disease consists of platinum-based chemotherapy, especially carboplatin-paclitaxel,[3] or hormonal therapy in case of low grade, hormone receptor positive tumors.[4, 5] There are no standard subsequent-line therapies. Five-year survival is only 10-20% for women with non-locally recurrent or metastatic disease.[2, 6-8] Consequently, new treatment strategies and paradigms are urgently needed for these patients. Among these, checkpoint inhibition and targeted therapies, such as Poly (ADP-ribose) polymerase (PARP) inhibition, are of interest with the current understanding of the molecular biology of endometrial cancer.

Here, we focus on the molecular basis of checkpoint and PARP inhibition in endometrial cancer and present an overview of the current and future clinical trials that investigate the potential of PARP- and checkpoint inhibition as mono- or combination therapy in advanced endometrial cancer and where relevant, other gynecological cancers. We also discuss the hypothesis of combination therapy induced synergistic anti-tumor effect and trials exploring the efficacy of this combination, such as the Durvalumab and Olaparib in Metastatic or recurrent Endometrial Cancer (DOMEC; NCT03951415) trial.

2. Molecular background

Significant progress in unraveling the underlying molecular biology of endometrial cancer has been made since the extensive molecular-genetic analysis by The Cancer Genome Atlas group (TCGA). The TCGA has identified four distinct molecular subgroups with prognostic significance:[9] (i) Endometrial cancer with pathogenic mutations in the exonuclease domain of DNA polymerase-epsilon (*POLE)* with an extremely high mutational load and an excellent prognosis; (ii) endometrial cancer with microsatellite instability (MSI) caused by mismatch repair deficiency with a high mutational load and an intermediate prognosis; (iii) a copy-number low (CNL) group with no specific molecular profile (NSMP), a low mutational load and an intermediate prognosis and; (iv) a group with frequent *TP53*-mutation characterized by extensive somatic copy-number alterations (SCNAs; CNH), a relatively low mutational load and a poor prognosis.

Subsequent studies have identified surrogate markers that can be used to classify endometrial cancer into four molecular subgroups analogous to the TCGA subclasses. This novel classification of endometrial cancer not only provides important prognostic information, it also yields biologically defined subgroups that may show different responses to specific drugs. For example, *POLE* ultramutated and mismatch repair deficient (MMRd) endometrial cancer are attractive candidates for immune checkpoint inhibition strategies, as they are associated with a high mutational burden and a prominent immune infiltrate.[10, 11] The immune checkpoint inhibitor pembrolizumab has been approved by the Food and Drug Administration (FDA) for unresectable or metastatic MSI or MMRd solid tumors. Secondly, CNH endometrial cancers are characterized by alterations in the actionable p53 pathway.[12, 13] This pathway alteration is associated with a high prevalence of homologous recombination deficiency (HRD).[14] Generally, HRD tumors are likely to respond to PARP inhibitors.[15] For patients with ovarian cancer and metastatic breast cancer PARP inhibitors are becoming part of standard-of-care therapy; PARP inhibition effect is largest in patients with *BRCA*-mutated tumors and those that are HRD.[16-21]

Research on differences between molecular alterations in primary and recurrent or metastatic endometrial cancer tumors is limited. In a Memorial Sloan Kettering Cancer Center (MSK) cohort, including 189 patients with recurrent and metastatic endometrial cancer analyzed for molecular characterization, the most frequent somatic alterations were similar to the TCGA cohort, although *TP53* mutations were more common and *PTEN* alterations were less common in the MSK cohort. These differences were largely explained by the histologic subtypes, with inclusion of carcinosarcomas and clear cell tumors and a higher proportion of serous and grade 3 tumors in the MSK cohort compared to the TCGA cohort.[22] Thus far, studies have indicated that the molecular classification according to TCGA subgroups is generally stable from primary to metastatic lesions.[22-24] However, in a small proportion of cases a shift from CNL to MMRd was seen[23] and *PTEN* mutations are less commonly observed in metastatic lesions compared to their matched primary tumor.[22] Gibson et al. found that abdominal metastases are more closely related to each other than to the primary tumor biopsy, so they might have arisen from a limited fraction of these cancers. Despite a notable heterogeneity between silent mutations of the primary tumor and their metastases, the overlap in non-silent mutations between the primary tumor and their metastases is large.[24]

Especially following therapy, derangements in multiple oncogenic or tumor-promoting pathways may occur. This should be considered when evaluating targeted therapies in the recurrent setting. Moreover, metastases to anatomical sites outside the abdominopelvic area might present with different actionable alterations. The large number of genetic co-alterations in advanced tumors can be a challenge in choosing targeted therapies.

Combining agents targeting different pathways attempts to circumvent these problems. Checkpoint and Poly (ADP-ribose) polymerase (PARP) inhibition are two promising treatment modalities for endometrial cancer. These agents can be combined, and it is hypothesized that this combination delivers a synergistic effect. This synergistic effect is discussed later in this review.

3. Checkpoint inhibition: anti-PD-(L)1 antibodies

Immune checkpoint inhibitors, particularly agents targeting the programmed cell death protein-1 (PD-1)/programmed death-ligand-1 (PD-L1) pathway, are being increasingly explored as a potential treatment strategy in various cancers. Checkpoint inhibition could prevent PD-1/PD-L1 interaction by blocking PD-1 or its ligand PD-L1.[25] The PD-1 receptor is a transmembrane protein expressed on the surface of activated T-cells.[26] Once PD-L1, commonly over-expressed on many tumor cells and hematopoietic cells, binds to PD-1 the immunological response is suppressed and apoptosis is inhibited. Checkpoint inhibition based on anti-PD-1/PD-L1 pathway antibodies can be subdivided in PD-1 blockers and PD-L1 blockers. PD-1 blockers which have established activity in several cancer types are nivolumab, pembrolizumab and cemiplimab.[27] PD-L1 blockers which have been shown to be effective are atezolizumab, avelumab and durvalumab. Theoretically, anti-PD-L1 has a less immune related toxicity profile compared to anti-PD-1, since they do not block binding of the other PD-1 ligand, PD-L2. PD-L2 is expressed on hematological cells, and interaction with PD-1 generates an inhibitory signal affecting the immune response. In addition, PD-L2 binds to repulsive guidance molecule b (RGMb), which regulates respiratory immunity.[28] No direct comparison has been made between PD-1 and PD-L1 inhibitors. Pembrolizumab has been approved by the FDA for unresectable or metastatic MSI or MMRd solid tumors that have progressed following prior treatment without satisfactory alternative treatment options, which include selected endometrial carcinomas.[29] Particularly tumors with a high mutational burden (e.g. *POLE*/MMRd subgroups) may be susceptible to PD-1/PD-L1 inhibitors.[30, 31] In endometrial cancer the MMRd subgroup are expected to benefit most, since *POLE* ultramutated endometrial cancer is associated with an extremely favorable prognosis and very rare disease recurrence.[12, 22] The PD-1 inhibitor dostarlimab is currently undergoing FDA review for advanced endometrial cancer.

The response to checkpoint inhibition seems to be more pronounced in patients with tumors that express PD-L1.[32-35] PD-L1 expression is higher among MMRd than MMR proficient endometrial cancer,[36, 37] although PD-L1 expression is not exclusive to the MMRd group.[38] The largest study on PD-L1 expression in endometrial cancer, including 700 patients, reported expression of PD-L1 in approximately 30% of MMRd tumors and less than 5% in MMR proficient tumors. Other studies report larger expression percentages

up to 53% in MMRd.[37, 39] Differences in reported percentages are probably explained by the heterogeneity in used methods and thresholds. There is no established cut-off for PD-L1 positivity in endometrial cancer. Although, in a basket trial enabling routine genomic testing for advanced cancer patients, the Strata Trial (NCT03061305), an RNA expression score of more than 22 (scale 0 -100) was validated as 100% sensitive and 70% specific for predicting PD-L1 tumor proportion score of ≥50%.[40] PD-L1 expression in lung cancer and breast cancer has proven to select patients that benefit most from checkpoint-inhibition, this has not yet been established for endometrial cancer.

The few trials published on PD-L1 or PD-1 inhibition in recurrent gynecological cancer showed clinical efficacy and an acceptable safety profile in endometrial cancer,[29, 41] cervical cancer[42] and ovarian cancer.[43-45] However, last update of the three-arm phase 3 JAVELIN Ovarian 100 and 200 trials in both patients with primary stage III or IV ovarian cancer and patients with platinum resistant or refractory ovarian cancer showed no significant difference in progression free survival (PFS) or overall survival (OS) after evaluating avelumab in combination with and/or following platinum-based chemotherapy, and avelumab with pegylated liposomal doxorubicin monotherapy, respectively.[46, 47] Le et al. [41] investigated pembrolizumab in patients with advanced MMRd cancers across 12 different tumor types. Of all tumor types, the highest frequency of MMRd was seen in endometrial cancer (17%). Objective response rate (ORR) was 53%, and complete responses were achieved in 21% of the 86 patients, of whom 15 had endometrial cancer. Pembrolizumab demonstrated a durable antitumor activity in 24 patients with heavily pretreated advanced PD-L1-positive endometrial cancer in the KEYNOTE-028.[29] Objective radiographic responses were observed in 13%, and stable disease also in 13%. No complete responses were observed and median PFS was 1.8 months (95% CI 1.6–2.7 months). Among all 19 tumor samples evaluable for MSI status the only tumor with MSI-high status had a partial response. The other two patients with a partial response had non-MSI-high status; one of them was *POLE*-mutated. This indicates that treatment effect is most pronounced in the MMRd subgroup, but it is not limited to this subgroup. Monotherapy is generally tolerated,[29, 35, 41-44, 48, 49] although awareness of immune-related adverse events is warranted.

Several phase 1 and 2 studies are currently recruiting patients with recurrent endometrial cancer to investigate anti PD-1 (NCT02628067, NCT02899793, NCT02728830, NCT03241745, NCT03474640, NCT02715284) or anti PD-L1 monotherapy (NCT03212404) in a single group design or compared to the combination with a monoclonal antibody against CTLA-4 in a randomized open label trial (NCT03015129). Two recruiting phase 3 trials are to investigate the addition of anti-PD-L1 therapy to the usual chemotherapy treatment (paclitaxel and carboplatin) in advanced or recurrent endometrial cancer (NCT03914612, NCT03981796).

4. PARP inhibition

Currently, PARP inhibitors are part of standard-of-care therapy for selected patients with ovarian cancer and metastatic breast cancer. PARP facilitates DNA damage repair in case of single-strand DNA breaks. Inhibition of PARP leads to accumulation of DNA damage and double-strand DNA breaks (DSBs). DSBs are repaired by two major pathways: homologous recombination repair and the more error prone 'nonhomologous end joining'. In patients whose tumors exhibit homologous recombination-deficiency (HRD), DNA repair is impaired and consequently these patients may be more sensitive to PARP inhibition.[15]

The various PARP inhibiting agents include olaparib, niraparib, rucaparib, talazoparib, and veliparib.[19] In December 2018, olaparib was approved as frontline maintenance therapy for germline *BRCA1/2* mutation associated ovarian cancer with response to platinum-based chemotherapy. Approval was based on the SOLO-1 trial,[50] that showed an improvement of median PFS after olaparib compared to placebo (49.9 versus 13.8 months, HR 0.30, 95% CI 0.23–0.41; $p < .01$). Recent phase 3 trials confirm the effectivity of PARP inhibition as frontline therapy after response to platinum-based chemotherapy[19] even in HR-proficient tumors (although to a lesser extent).[20] Moreover, olaparib, niraparib and rucaparib have been approved for maintenance therapy in patients with recurrent ovarian cancer regardless of *BRCA*-status, who responded to platinum-based chemotherapy based on the SOLO-2, NOVA and ARIEL-3 trials.[16-18] In addition, olaparib and talazoparib have received FDA approval for treating patients with *BRCA*-mutated metastatic breast cancer, based on PFS improvement in the phase 3 EMBRACA[51] and OlympiAD trials.[52] Adverse events, including fatigue, gastro-intestinal and hematologic adverse events, were generally acceptable and manageable with dose modifications and delays.[16-21, 50-52] An overview of these studies is displayed in Appendix Table A1.

The hypothesized benefit of PARP inhibition in endometrial cancer is based on the observed effect in *BRCA1/2* mutated and HRD tumors mentioned above. Whether endometrial cancer should be considered part of germline *BRCA*-associated syndrome is under debate.[53] Nevertheless, previous research pointed out molecular similarities of serous-like/SCNA-high endometrial cancer and both basal-like breast cancer and high-grade serous ovarian cancer, including a high number of SCNAs and frequent *TP53* mutations.[12] Serous-like/SCNA-high endometrial cancers also frequently are HRD.[14] In general, HRD tumors are sensitive to platinum-based chemotherapy and PARP inhibitors.[54, 55]

Currently, no clinical trials on PARP inhibition in endometrial cancer have been published. However, there are three upcoming or currently recruiting trials in recurrent or metastatic endometrial cancer. In a single group phase 2 trial, the efficacy of niraparib is being

investigated in 44 patients (NCT03016338). Two planned randomized placebo-controlled trials will investigate the activity of rucaparib (NCT03617679) and olaparib (NCT03745950) in respectively 138 and 147 patients with metastatic endometrial cancer.

5. Combination therapy

There is growing interest in combining immunotherapy with other targeted agents and with chemotherapy in all endometrial cancer subtypes. However, only one clinical trial combining immunotherapy with other targeted therapy in endometrial cancer has been published. Makker and Taylor et al.[56, 57] investigated the combination of pembrolizumab and lenvatinib, a multikinase inhibitor targeting VEGFR, FGFR, and PDGFR in a phase 2 study in selected solid tumors, including endometrial cancer, irrespective of MMRd or PD-L1 expression status. Grade 3 or higher treatment related adverse events occurred in 67–68%. Dose interruptions (70%) or dose reductions (63–64%) were needed to manage adverse events in the majority of patient; 15–16% of the patients discontinued the study due to adverse events.[56, 57] The ORR at 24 weeks among the 108 patients with metastatic endometrial cancer was 38% (95% CI 29–48%) and median PFS was 7.4 months (95% CI 5.3–8.7).[57] ORRs for participants with MMRd (94 patients) and MMR proficient (11 patients) endometrial cancer were 36% and 64%, respectively. As a result of the high anti-tumor activity the FDA has approved this combination for metastatic endometrial cancer that is not MSI-H or MMRd in September 2019. Two randomized phase 3 trials (KEYNOTE-775/NCT03517449, ENGOT-EN9/LEAP-001/NCT03884101) are currently recruiting.

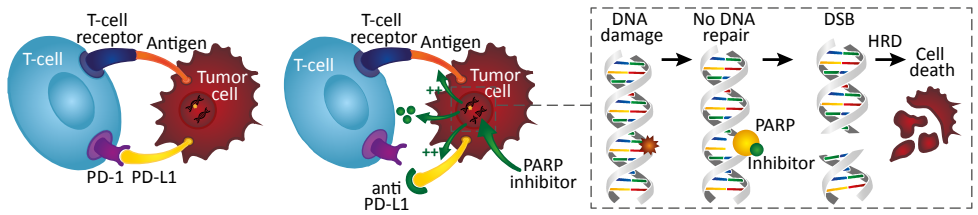

Figure 1. Effect of anti-PD-L1 and PARP inhibition.
Interaction of PD-1 and PD-L1 inhibts cytotoxic T lymphocytes (CTLs) activity, allowing the cancer cells to escape immune detection. Poly (ADP-ribose) polymerase (PARP) inhibitors and anti-PD-L1 antibodies synergize and may enhance an antitumor immune response mediated by specific activated CTLs against tumor antigens. Inhibition of PARP leads to accumulation of DNA damage and double-strand DNA breaks (DSBs). In patients whose tumors exhibit homologous recombination-deficiency (HRD), DNA repair is impaired which can lead to apoptotic death. In addition, DNA damage due to PARP inhibition causes upregulation of chemokines and neo-antigen expression (green arrows) and induces an immune response mediated by CTLs. Anti-PD-L1 can reverse the potential immune escape of tumor cell mediated by the PD-L1 upregulation induced by PARP inhibitors. *Reprinted with permission from Ned Tijdschr Oncol 2019;14:(8).*

Both PARP inhibition and PD-1/PD-L1 inhibition have the potential to show activity in specific subgroups of endometrial cancer as monotherapy. The combination of these two agents is promising and currently being investigated among several tumor types (Table 1). Preclinical studies have shown that the combination can have additive or even synergistic effects. The accumulation of DNA damage caused by PARP inhibition may complement anti-tumor activity of immune checkpoint blockade by expanding neoantigen expression and greater immune recognition of the tumor.[58-60] *In vitro* and *in vivo* breast cancer models have shown that PARP inhibitors inactivate glycogen synthase kinase 3, which in turn up-regulates PD-L1 expression.[61] Another study does not show upregulation of PD-L1 expression, although high PD-L1 expression was seen in the models that did not respond to PARP inhibition.[62] Checkpoint inhibition can theoretically restore antitumor immunity and enhance the antitumor activity of PARP inhibitors (Figure 1). The benefit may be expected the most in *TP53* mutated endometrial cancer. Moreover, a substantial part of MMRd tumors harbor one or more mutations in key components of the cellular DNA damage response pathway such as At-rich interactive domain 1A (ARID1A) or meiotic recombination 11 (MRE11),[63, 64] which may sensitize cancer cells to PARP inhibitors.[65] Together, although data is still limited, these preclinical studies support the potential added (or even synergistic) effect of combining PARP inhibitors and checkpoint inhibitors.

There are only few published clinical trials on combined checkpoint and PARP inhibition, predominantly in ovarian cancer. The recently published phase 1/2 TOPACIO study showed promising response to niraparib combined with pembrolizumab in triple negative breast cancer or ovarian cancer, irrespective of *BRCA* mutation status or PD-L1 expression. They reported an ORR of 18% and a disease control rate (DCR) of 65% in 62 patients with ovarian cancer and respectively 21% and 49% in 55 patients with triple negative breast cancer.[66, 67] A dose-escalation phase 1 trial by Jung-Min et al.[68] reported an ORR of 17% and a DCR of 83% without any dose-limiting toxicity with the durvalumab-olaparib combination in 12 patients with ovarian cancer or triple negative breast cancer. Preliminary results of the first 32 *BRCA* mutated platinum-sensitive relapsed ovarian cancer patients in the MEDIOLA-trial showed promising efficacy with a particularly high ORR of 72% with a total of seven complete responses. Most common grade 3 or higher adverse events were anemia (17.6%), elevated lipase (11.8%), neutropenia (8.8%), and lymphopenia (8.8%). Five patients discontinued olaparib and three discontinued durvalumab due to an adverse event.[69, 70] This treatment regimen also demonstrated efficacy and acceptable toxicity in metastatic castration-resistant prostate cancer.[71] In the randomized phase 3 JAVELIN Ovarian PARP 100 trial patients with primary stage III or IV ovarian cancer were randomized to chemotherapy and avelumab followed by maintenance avelumab and talazoparib versus an active comparator. Despite a good safety profile, efficacy interim analysis did not support continuation of the avelumab-talazoparib combination in an unselected patient population.[72]

Several studies are ongoing to investigate the safety and efficacy of combining PARP inhibition and PD-1/PD-L1 pathway inhibition in gynecological cancers. The current recruiting studies are displayed in Table 1. Three of these studies include patients with recurrent or persistent endometrial cancer. The open-label two-group phase 2 study (NCT02912572) [73] is designed for 70 patients previously treated with at least one line of chemotherapy. Cohort-1, including MSI-H and/or *POLE*-mutant endometrial cancers, are to receive avelumab monotherapy. Cohort 2, which includes microsatellite stable tumors with negative or unknown *POLE*-mutation status, will receive the combination therapy of avelumab and talazoparib. Secondly, the combination of PARP inhibition with a PD-1 blocker is investigated in a phase 1/2 study among 60 patients with either recurrent endometrial cancer or castration resistant prostate cancer (NCT03572478).

The combination of PARP inhibition and PD-L1 blocking is investigated among all molecular subgroups of endometrial cancer in the DOMEC trial (NCT03951415; Figure 2). This study has been initiated by the Dutch Gynecological Oncology Group. It is a multi-center, single arm phase 2 trial for 55 patients with metastatic, refractory or recurrent endometrial cancer (including carcinosarcoma) to investigate the efficacy of the combination therapy of olaparib and durvalumab. Patients who have not responded to or who have relapsed after at least one prior line of chemotherapy or who are not able/willing to get chemotherapy are eligible for the study. The primary endpoint is PFS.

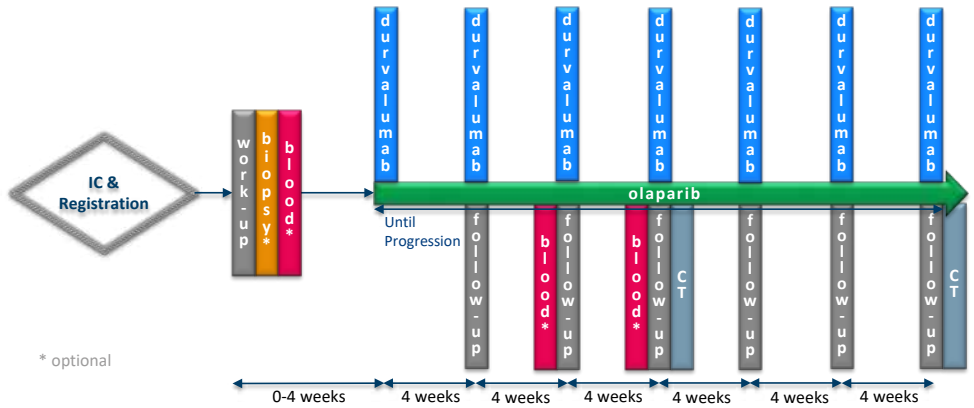

Figure 2. Participant timeline DOMEC-trial.
CT = CT scan of the abdomen and chest (or MRI when indicated); IC = Informed consent; Work-up consists of: history, physical examination, blood including chemistry and hematology, electrocardiogram and imaging; Follow-up consists of: history, physical examination, blood chemistry and hematology.
*Optionally an additional blood sample for immune-monitoring or an additional fresh frozen biopsy.

Table 1. Ongoing trials combining PARP inhibitors and PD-L1/PD-1 pathway inhibitors in gynecological cancers

Drug	NCT number Acronym	Conditions		*N*	Phase	Design	Country
Olaparib + Durvalumab	NCT03951415 DOMEC	RP	Advanced Endometrial Cancer	55	2	Single Group	NL
	NCT03737643 DUO-O	ND	Advanced OC	1056	3	Randomized Blinded	US + 15
	NCT03699449 AMBITION	RP	Platinum-resistant OC	68	2	Randomized Open Label	KR
	NCT02734004 MEDIOLA	RP	Advanced Solid tumors (incl. OC)	427	1/2	Single Group	US + 6
Avelumab + Talazoparib	NCT02912572	RP	Advanced Endometrial Cancer (cohort2: MSS)	70	2	Non-Randomized Open label	US
	NCT03330405	RP	Locally Advanced or Metastatic tumors	242	2	Sequential Open label	US + 6
Rucaparib + nivolumab	NCT03572478	RP	Advanced Endometrial Cancer (and CRPC)	60	1b/2a	Single Group / Randomized	US
	NCT03522246 ATHENA	ND	Platinum-responsive Advanced OC	1012	3	Randomized Blinded	US + 8
	NCT03824704	RP	OC*	139	2	Non-Randomized Open label	US
Niraparib + TSR-042	NCT03602859 FIRST	ND	Advanced OC	960	3	Randomized Blinded	US + 8
	NCT03574779 OPAL	ND RP	High-grade OC	40	2	Single group	US
Niraparib + Atezolizumab	NCT03598270 ANITA	RP	Advanced OC	414	3	Randomized Blinded	ES
Rucaparib + Atezolizumab	NCT03101280	RP	Advanced OC and TNBC	48	1	Non-Randomized Open Label	AU + 3

Several studies have multiple treatment arms to compare to standard treatment, mono therapy and/or other novel drug combinations. Advanced disease is defined as stadium III-IV; AU = Australia; BC = breast cancer; BE = Belgium; CRPC = castrate-resistant prostate cancer; ES = Spain; KR = Korea; TNBC = triple negative breast cancer; NL = the Netherlands; MSS = microsatellite stable ND = newly diagnosed; OC = ovarian cancer; RP = recurrent or persistent; US = United States.
*or locally advanced unresectable/metastatic transitional cell urothelial carcinoma

6. Conclusion

In conclusion, both PARP inhibitors and checkpoint inhibitors are promising effective novel modalities in cancer treatment. PARP inhibitors are part of standard-of-care therapy for ovarian cancer and metastatic breast cancer. Checkpoint inhibition by anti-PD-1/PD-L1 pathway antibodies is indicated for unresectable or metastatic MSI or MMRd solid tumors. Combining these agents in the treatment of recurrent and metastatic endometrial cancer seems promising as these agents may have a synergistic effect. This combination is currently investigated in phase 2 setting. Depending on the results of those studies subsequent phase 3 trials of PARP and checkpoint inhibition in advanced endometrial cancer will be conducted.

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APPENDIX A

A1. Search strategy

A comprehensive search in PubMed and clinicaltrials.gov was performed for clinical studies published or posted in English on February 28, 2019, with the terms and synonyms of "gynecological cancer" OR "endometrial cancer" OR "ovarian cancer" OR "cervical cancer" OR "breast cancer" AND "PARP inhibitor" OR "checkpoint inhibitor". References of relevant records were also evaluated for cross-referencing. We identified 5 relevant (phase 3) trial publications for PARP inhibition monotherapy (0 in endometrial cancer), 8 relevant (phase 1-2) published trials for PD-1/PD-L1 blocking monotherapy (2 in endometrial cancer) and 1 relevant (phase 1) trial publication for the combination therapy (0 in endometrial cancer). An updating PubMed search was performed on May 22, 2019, resulting 1 additional relevant (phase 2) trial publication for PARP or checkpoint inhibitor combined with another immunotherapy or targeted therapy agent in endometrial cancer. A last update was done on August 15, 2019 resulting in addition of the TOPACIO trial publications (combined treatment in ovarian and breast cancer). Finally, relevant abstracts presented at ESMO Congress 2019 were included in the manuscript.

Table A1. Overview of phase 3 PARP inhibition studies in gynecological cancer and breast cancer

	Conditions						
	BRCAm			***N***	**Phase**	**Agents**	**endpoint**
SOLO-1 *Moore, 2018*	ND	+	OC*	391	3	Olaparib vs placebo (2:1)	mPFS 49.9 vs 13.8m; HR 0.30 (0.23-0.41); *p*<0.01
SOLO-2 *Pujade, 2019*	RP	+	OC	295	3	Olaparib vs placebo (2:1)	mPFS 19.1 vs 5.5m; HR 0.30 (0.22-0.41); *p*<0.01
NOVA *Mirza, 2016*	RP	+/-	OC	553	3	Niraparib vs placebo (2:1)	BRCA+: mPFS 21.0 vs 5.5m; HR 0.27 (0.17-0.41) BRCA-, HRD: mPFS 12.9 vs 3.8m; HR 0.38 (0.24-0.59) BRCA-: mPFS 9.3 vs 3.9m; HR 0.45 (0.34-0.61) *p*<0.01
ARIEL-3 *Coleman, 2017*	RP	+/-	OC	564	3	Rucaparib vs placebo (2:1)	BRCA+: mPFS 16.6 vs 5.4m; HR 0.23 (0.16-0.34); HRD: mPFS 13.6 vs 5.4m; HR 0.32 (0.24-0.42); BRCA+/-: mPFS 10.8 vs 5.4m; HR 0.37 (0.30-0.45); *p*<0.01
VELIA *Coleman, 2019*	ND	+/-	OC	1140	3	CT + veliparib followed by placebo / veliparib vs CT + placebo followed by placebo (1:1:1)	BRCA+: mPFS 34.7 vs 22.0 HR 0.44 (0.28-0.68) HRD: mPFS 31.9 vs 20.5 HR 0.57 (0.43-0.76) *p*<0.01 HRP: HR 0.81 (0.60-1.09)
PRIMA *González, 2019*	ND	+/-	OC*	733	3	Niraparib vs placebo (2:1)	HRD: mPFS 21.9 vs 10.4 HR 0.43 (0.31-0.59) HRP: HR 0.68 (0.49-0.94)** *p*<0.01
PAOLA-1 *Ray-Coquard, 2019*	ND	+/-	OC	806	3	Olaparib + bevacizumab vs placebo + bevacizumab (2:1)	BRCA+: mPFS 37.2 vs 21.7 HR 0.31 (0.20-0.47) BRCA-: mPFS 28.9 vs 16.0 HR 0.71 (0.58-0.88) BRCA+, HRD: mPFS 37.2 vs 17.7 HR 0.33 (0.25-0.45) BRCA0, HRD: mPFS 28.1 vs 16.6 HR 0.43 (0.28-0.66) HRP/unk: mPFS16.9 vs 16.0 HR 0.92 (0.72-1.17)
EMBRACA *Litton, 2018*	RP	+	BC	431	3	Talazoparib vs physician's choice single agent (2:1)	mPFS 8.6 vs 5.6m; HR 0.54 (0.41-0.71); *p*<0.01
OlympiAD *Robson, 2017*	RP	+	BC	302	3	Olaparib vs physician's choice single-agent (2:1)	mPFS 7.0 vs 4.2m; HR 0.58 (0.43-0.80); *p*<0.01

BC = breast cancer; BRCA+ = breast cancer gene mutation; BRCA- = no breast cancer gene mutation; CT = chemotherapy with carboplatin and paclitaxel; HR = hazard ratio; HRD = homologue recombinant deficient; HRP = homologue recombinant Proficient; m = months; mPFS = median progresion free survival; ND = newly diagnosed; OC = ovarium cancer; RP = recurrent or persistent.

* Advanced OC after complete/partial response platinum-based chemotherapy.

** NB In the homologue recombinant not determined group the hazard ratio was 0.83 (0.51-1.43).

A2. Design and eligibility criteria of the DOMEC-trial

Summary

The Durvalumab and Olaparib in Metastatic or recurrent Endometrial Cancer (NCT03951415; DOMEC) trial has been initiated by the Dutch Gynecological Oncology Group. The study is designed as a prospective, multi-center, single arm phase II study for 55 patients with metastatic, refractory or recurrent endometrial cancer (including carcinosarcoma of the uterus) to investigate the efficacy of the combination therapy of olaparib 300mg PO BID and durvalumab 1500mg IV q4w. Patients who have not responded to or who have relapsed after at least one prior line of chemotherapy or who are not able/willing to get chemotherapy are eligible for the study. The primary endpoint is progression free survival (PFS). Efficacy is defined as a median PFS of 6 months (compared to the estimated 30% PFS at 6 months without treatment). Forty-six evaluable patients are needed to test the null hypothesis according to Simon's two-stage design. With an expected drop-out rate of 20%, 55 patients will be entered into the trial. Interim analysis will be performed on the first 15 evaluable patients. Secondary endpoints include objective response rate (ORR) according to RECIST 1.1 criteria; overall survival (OS); adverse events assessed by NCI Common Terminology Criteria for adverse Events (CTCAE) version 5.0; and predictive biomarkers. Optional secondary endpoints are: baseline HRD assay and immunological effects of PARP-1 inhibition measured by tests for T cell and APC functionality and predictive biomarkers for PD-L1 blocking in blood. Baseline assessment consists of medical history including toxicity assessment, blood chemistry, hematological screening, a pregnancy test (in women of child-bearing potential), ECG, imaging (e.g. CT thorax/abdomen or MRI) and complete physical examination (incl. height, weight, WHO performance status and vital signs). Diagnosis will be centrally confirmed by the LUMC's Department of Pathology. Extra tumor biopsies will be performed for RAD51 testing (only at baseline) and at 3 times blood samples for immunomonitoring (50cc) will be taken; patients will be able to opt out of the extra biopsies and/or blood samples. Every 4 weeks during treatment and at completion of therapy physical examination, blood chemistry and hematology and imaging will be performed. Three months after last treatment, WHO performance status, hematology, chemistry and tumor assessment will be reported. Participant timeline is schematically shown in *Article Figure 2*. Treatment will be continued until disease progression, patient's request to discontinue or unacceptable toxicity. Total recruitment time is assumed to be 30 months. Follow-up after inclusion of the last subject will be 6 months, resulting in a total study duration of 36 months.

Eligibility criteria

To be eligible for the DOMEC-trial, patients must be (1) at least 18 years old, (2) have a WHO performance score of 0-1, and (3) have histologically confirmed diagnosis of EC (including carcinosarcoma of the uterus). There must be (4) a documented progressive disease (metastatic or locally advanced) according to RECIST 1.1 criteria. (5) Disease must be not amendable to local therapy, chemotherapy and hormonal therapy (or patient is not be able/willing to get chemotherapy). (6) Organ system function should be adequate, defined as adequate bone marrow function (Haemoglobin ≥ 10.0 g/dL, Absolute neutrophil count (ANC) ≥ 1.5 x 10^9 /L, Platelet count ≥ 100 x 10^9 /L), liver function (Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN), Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) ≤ 2.5 x ULN (in case of lever metastases ≤ 5x ULN) and kidney function (creatinine clearance ≥51 mL/min calculated according to Cockcroft-Gault or 24 hour urine clearance). (7) Life expectancy must be at least 16 weeks.

Patients with (1) history of leptomeningeal carcinomatosis, symptomatic brain metastases (uncontrolled despite of corticosteroids) or spinal cord compression are not eligible. Other exclusion criteria are (2) severe concomitant diseases; (3) active or prior documented autoimmune or inflammatory disorders; (4) active primary immunodeficiency; (5) active infections including tuberculosis, HIV, hepatitis B or C or (6) other malignant disease (except adequately treated non-melanoma skin cancer, lentigo maligna or carcinoma in situ without evidence of disease). (7) Prior treatment with PARP, PD1 or PD-L1 inhibitor; (8) prolonged QTc interval or family history of long QT syndrome; (9) severe psychiatric illness; (10) irreversible grade ≥2 toxicity from previous anti-cancer therapy; (11) major surgery in the last 2 weeks; (12) prior allogeneic bone marrow transplantation or double umbilical cord blood transplantation; (13) inability to swallow oral medication; (14) concurrent treatment with another investigational agent during the conduct of the trial or (15) known intolerance to olaparib or durvalumab will prohibit inclusion; as well as (16) pregnancy or breast feeding.

For more details see https://clinicaltrials.gov/ct2/show/NCT03951415.

Chapter 6

Efficacy and safety of durvalumab with olaparib in metastatic or recurrent endometrial cancer (phase 2 DOMEC trial)

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ABSTRACT

Background

Patients with advanced endometrial cancer have a poor prognosis, and treatment options are limited. The investigator-initiated, multicenter, phase 2 DOMEC trial (NCT03951415) is the first trial to report data on efficacy and safety of combined treatment with PD-L1 and PARP inhibition for advanced endometrial cancer.

Patients and methods

Patients with metastatic or recurrent endometrial cancer were enrolled. Patients received durvalumab 1500 mg intravenously q4w and olaparib 300 mg 2dd until disease progression, unacceptable toxicity, or patient withdrawal. Patients with at least 4 weeks of treatment were evaluable for analysis. The primary endpoint was progression-free survival at 6 months. Evidence for efficacy was defined as progression-free survival at 6 months in ≥50% of patients. Secondary endpoints included safety, objective response and overall survival.

Results

From July 2019, through November 2020, 55 patients were enrolled. At data cut-off (September 2021), 4 of the 50 evaluable patients were still on treatment. Seventeen patients (34%) were progression-free at 6 months. Objective response rate was 16% (95% CI 8.3 to 28.5) with 1 complete and 7 partial responses. With a median follow-up of 17.6 months, median progression-free survival was 3.4 months (95% CI 2.8 to 6.2) and median overall survival was 8.0 months (95% CI 7.5 to 14.3). Grade 3 treatment-related adverse events occurred in 8 patients (16%), predominantly anemia. There were no grade 4 or 5 treatment-related adverse events.

Conclusions

The combination of durvalumab and olaparib was well tolerated, but did not meet the prespecified 50% 6-month progression-free survival in this heterogeneous patient population with advanced endometrial cancer.

Introduction

Endometrial cancer is the most common gynecological cancer in developed countries. Treatment options for advanced disease after initial platinum-taxane based chemotherapy, and endocrine therapy in case of hormone receptor positive tumors, are scarce.[1-6] Recently, immunotherapy using checkpoint inhibition has been studied and registered as monotherapy[7-12] and in combination with angiogenesis inhibition[5, 6] with promising response rates.

The endometrial cancer molecular classification introduced by The Cancer Genome Atlas[13] provides a basis for individualized risk stratification and treatment. The significant prognostic and predictive differences among the four molecular subgroups in early-stage disease have been replicated in standard diagnostic pathology materials using surrogate markers, identifying similar subgroups: p53-abnormal (p53abn), *POLE*-ultramutated, mismatch repair-deficient or microsatellite unstable (MMRd), and no specific molecular profile (NSMP) endometrial cancer.[14-16] However, predictive significance in recurrent/advanced setting has not been well characterized to date.

MMRd advanced endometrial cancer, which is characterized by a high number of somatic mutations and increased immunogenicity, has been shown to potentially benefit from single-agent programmed cell death-ligand or protein 1 (PD-[L]1) inhibitors with reported objective tumor response rates varying between 27% and 57%.[7-11] Nevertheless, the majority of advanced endometrial cancers will likely be relatively resistant to single-agent checkpoint inhibitors.[10-12] Inducing an immune response to checkpoint inhibitors by combining them with other treatment modalities may be a more rational approach for these tumors.[5, 6, 17]

Poly (ADP-ribose) polymerase (PARP) inhibition has been raising interest as treatment modality in endometrial cancer. As monotherapy, particularly in the molecular subgroup with the worst clinical outcome: p53abn endometrial cancer, in which homologous recombination deficiency (HRD) has been reported.[18, 19] Moreover, the combination of checkpoint inhibition with PARP inhibition has the potential of synergy and thus might be of interest in all types of advanced endometrial cancer. The accumulation of DNA damage caused by PARP inhibition may complement anti-tumor activity with alteration in immune-checkpoint receptor expression that could predispose to response to checkpoint inhibition.[17, 20] The combination of checkpoint inhibition plus PARP inhibition has already been shown to be safe with promising activity in phase 1 and 2 trials,[21, 22] but has not been studied before in endometrial cancer.

The phase 2 DOMEC trial was initiated to investigate the efficacy and safety of combined immune-checkpoint and PARP inhibition for patients with metastatic, persistent or recurrent endometrial cancer.

Methods

Study design and patients

The DOMEC trial was an investigator-initiated multicenter, open-label, single-arm phase 2 study (ClinicalTrials.gov identifier: NCT03951415) of the Dutch Gynecology Oncology Group (DGOG) evaluating the efficacy and safety of combination treatment with durvalumab and olaparib in patients with advanced (recurrent, persistent or metastatic) endometrial cancer. Patients were enrolled at 7 sites in the Netherlands. Data were collected from the first registry date, July 9, 2019, through September 24, 2021. Women with histologically confirmed endometrial cancer including uterine carcinosarcoma were eligible if they had received at least one prior platinum-based chemotherapeutic regimen or were not able or willing to receive chemotherapy. Eligible patients should have documented progressive disease not amenable to local therapy or endocrine therapy, measured by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria before enrollment. Other key eligibility criteria included WHO performance status 0 or 1, adequate organ function, no previous treatment with PARP inhibitor or PD-(L)1 inhibitor, and no other active primary malignancy. Inclusion was irrespective of molecular subtype. Detailed eligibility criteria are described in Appendix A1. Written informed consent was obtained from all patients prior to enrollment. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and the protocol was approved by the Ethics Committee (METC LDD) and the institutional review board of each participating clinical site. Study drugs and an unrestricted grant were supplied by AstraZeneca.

Procedures and outcomes

Patients received durvalumab 1500 mg intravenously once every 4 weeks and olaparib tablets 300 mg twice daily orally until disease progression, treatment discontinuation due to toxicity, or patient withdrawal of consent. Disease progression was based on RECIST v1.1 or documented clinical progression. Radiographic tumor assessment by CT or MRI was performed every three months and at the end of treatment. If radiologic imaging showed disease progression by RECIST v1.1 while the patient was clinically stable and had clinical benefit, study treatment could be continued awaiting radiologic confirmation of disease progression 4 weeks later. Secondary tumor assessment according to irRECIST criteria was performed to account for delayed response and pseudo-progression. Progression-free survival (PFS) was defined as the time from registration to the first documented disease progression or death from any cause; overall survival (OS) was defined as the time from registration to the date of death from any cause; objective response (OR) was defined as a confirmed complete or partial response (best response from study start until the end of treatment) using RECIST v1.1. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. The primary endpoint was PFS at 6 months (PFS6). Secondary endpoints included PFS, OS, OR, and safety of combined durvalumab and olaparib.

Central pathology revision was performed after registration. Estrogen receptor (ER) immunohistochemical staining with a 10% cut-off was performed. Tumors were classified according to the diagnostic algorithm of the molecular classification of endometrial cancer;[23] KASPar competitive allele-specific polymerase chain reaction (LGC Genomics, Berlin, Germany) was performed to screen for *POLE* hotspot variants at codons 286, 297, 411, 456, and 459, and immunohistochemical staining of p53 and MMR proteins (PMS2 and MSH6)[24, 25] were performed as previously described.[16]

Statistical analysis

Simon's optimal two-stage design was used with 15 patients evaluable for efficacy in the first phase. If there were at least 6 patients with PFS6, the additional 31 patients would be enrolled in the second stage for 46 evaluable patients. With an expected drop-out of 20%, 55 patients had to be enrolled in the trial. Evidence for sufficient efficacy would be PFS6 in at least 50% of patients, which is equivalent to a median PFS of at least 6 months. Assuming a baseline PFS6 of 30% and improved PFS6 of 50%, this study had 80% power at a 5% significance level.

The data cut-off date was September 24, 2021. Baseline characteristics, safety and efficacy results were summarized descriptively. All evaluable patients, defined as having at least 28 days (1 cycle) of treatment, were included in the primary analysis. PFS and OS were evaluated with the Kaplan-Meier method. Patients who did not experience a PFS or OS event were censored at their last assessment. Subgroup analyses for molecular group, histology and responders versus non-responders were performed using Fisher's exact test, Mann-Whitney U test and log-rank test.

Results

Patients

Between July 9, 2019, and November 25, 2020, 55 patients with advanced endometrial cancer from 7 sites in the Netherlands were enrolled. The drop-out rate was lower than expected, providing 50 patients evaluable for efficacy and safety analysis (Figure 1). The median age of evaluable patients was 69.0 years (IQR 64.3 to 73.0), and the majority had

received prior chemotherapy (42/50, 84%) and/or endocrine therapy (13/50, 26%). The most common histologic subtypes of disease were serous carcinoma (38%), endometrioid adenocarcinoma (32%; International Federation of Gynecology and Obstetrics [FIGO] grade 1 or 2, 20%; FIGO grade 3, 12%), clear cell carcinoma (12%) and carcinosarcoma (14%). Twenty-nine (58%) tumors were classified as p53abn, 10 (20%) as MMRd, 10 (20%) as NSMP and none as *POLE*mut endometrial cancer (Table 1). Two of the NSMP endometrial cancers were ER-positive.

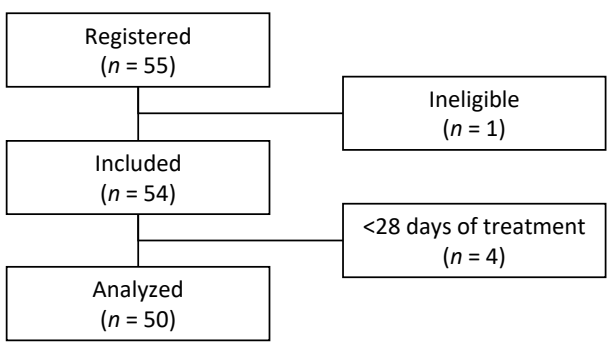

Figure 1. CONSORT diagram of study enrollment

Efficacy

Among the 50 evaluable patients, 17 patients (34%) were free from progression at 6 months (18 [36%] when using irRECIST), and thus did not meet the predefined threshold of 50% 6-month PFS. Under the hypothesis of 50% 6-month PFS, the probability of having 17 out of 50 patients with PFS6, the *p*-value for Simon's two-stage design, equals 0.016. The median follow-up time was 17.6 (95% CI 10.1 to 20.2) months. Median PFS was 3.4 months (95% CI 2.8 to 6.2; Figure 2A) and median OS was 8.4 months (7.5 to 14.3; Figure 2B). Median PFS for low-grade endometrial cancer patients was 4.2 months (95% CI, 3.0 to NR) and for high-grade endometrial cancer patients 3.4 months (2.8 to 7.8; $p = .82$; Figure 2C). When compared by molecular subgroup, median PFS for MMRd endometrial cancer patients was 5.7 months (95% CI 2.8 to NR), for NSMP 3.2 months (2.6 to NR), and for p53abn 3.0 months (2.8 to 7.8; $p = .67$; Figure 2D).

There was objective response in 8 out of 50 patients (ORR 16%, 95% CI 8.3 to 28.5; Table 2 and Figure 3A); One patient (2%) had a confirmed complete response (CR), and 7 patients (14%) had a confirmed partial response (PR). There were no significant differences when using irRECIST. Four patients were still receiving protocol treatment at the data cut-off date (Figure 3B).

Table 1. Baseline characteristics

Characteristics	*N* = 50
Median age (IQR), years	69.0 (64.3, 73.0)
Median BMI (IQR)	27.9 (22.4, 31.5)
WHO performance status	
0	13 (27.7)
1	34 (72.3)
Histologic subtype	
Endometrioid EC Grade 1/2	10 (20.0)
Endometrioid EC Grade 3	6 (12.0)
Serous EC	19 (38.0)
Clear Cell Carcinoma	6 (12.0)
Carcinosarcoma	7 (14.0)
Undifferentiated EC	2 (4.0)
Molecular classification	
p53-abnormal EC	29 (59.2)
MMRd EC	10 (20.4)
NSMP EC	10 (20.4)
*POLE*mut EC	0 (0.0)
Hormonal status	
ER positive	23 (46.9)
ER negative	26 (53.1)
Prior chemotherapy	42 (84.0)
Number of lines chemotherapy	
1	29 (69.0)
2	11 (26.2)
3	2 (4.8)
Prior endocrine therapy	13 (26.0)
Number of lines endocrine therapy	
1	8 (66.7)
2	3 (25.0)
5	1 (8.3)
Prior radiotherapy	34 (68.0)

NOTE. Data reported as No. (%) unless otherwise indicated.

EC = endometrial cancer; ER = estrogen receptor; MMRd = mismatch repair deficiency; NSMP = non-specific molecular profile; *POLE*mut = *POLE*-ultramutated; WHO = World Health Organization.

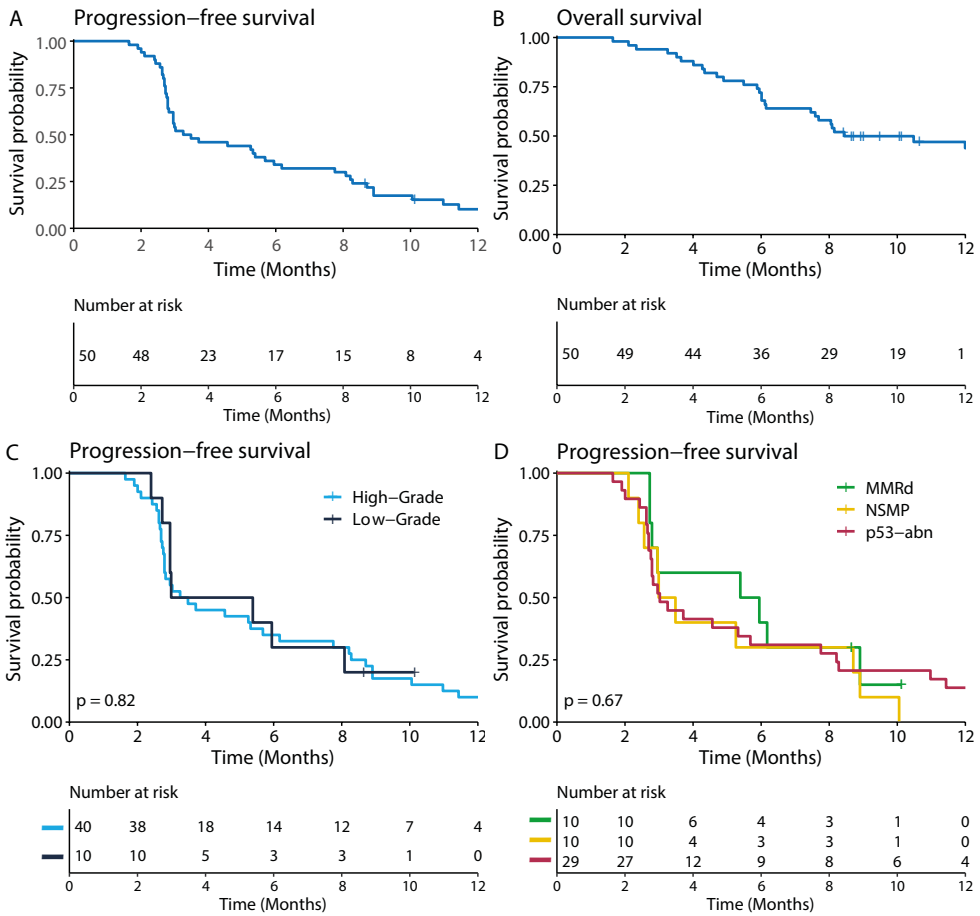

Figure 2. Kaplan-Meier curves for progression-free survival (A) and overall-survival (B) of the evaluable population, and progression-free survival by histological subtype (C) and molecular subgroup (D). MMRd = mismatch repair deficiency; NSMP = non-specific molecular profile; p53-abn = p53-abnormal.

There were no significant differences in characteristics between responders and non-responders. Objective response to treatment was seen in 6 tumors classified as p53abn and 2 classified as MMRd endometrial cancer. The three patients in whom *BRCA 1* germline mutations were already known all showed objective response (1 CR with progression after 12.9 months, 1 PR with progression after 8.3 months and 1 PR who was still receiving protocol treatment at data cut-off after 20 months).

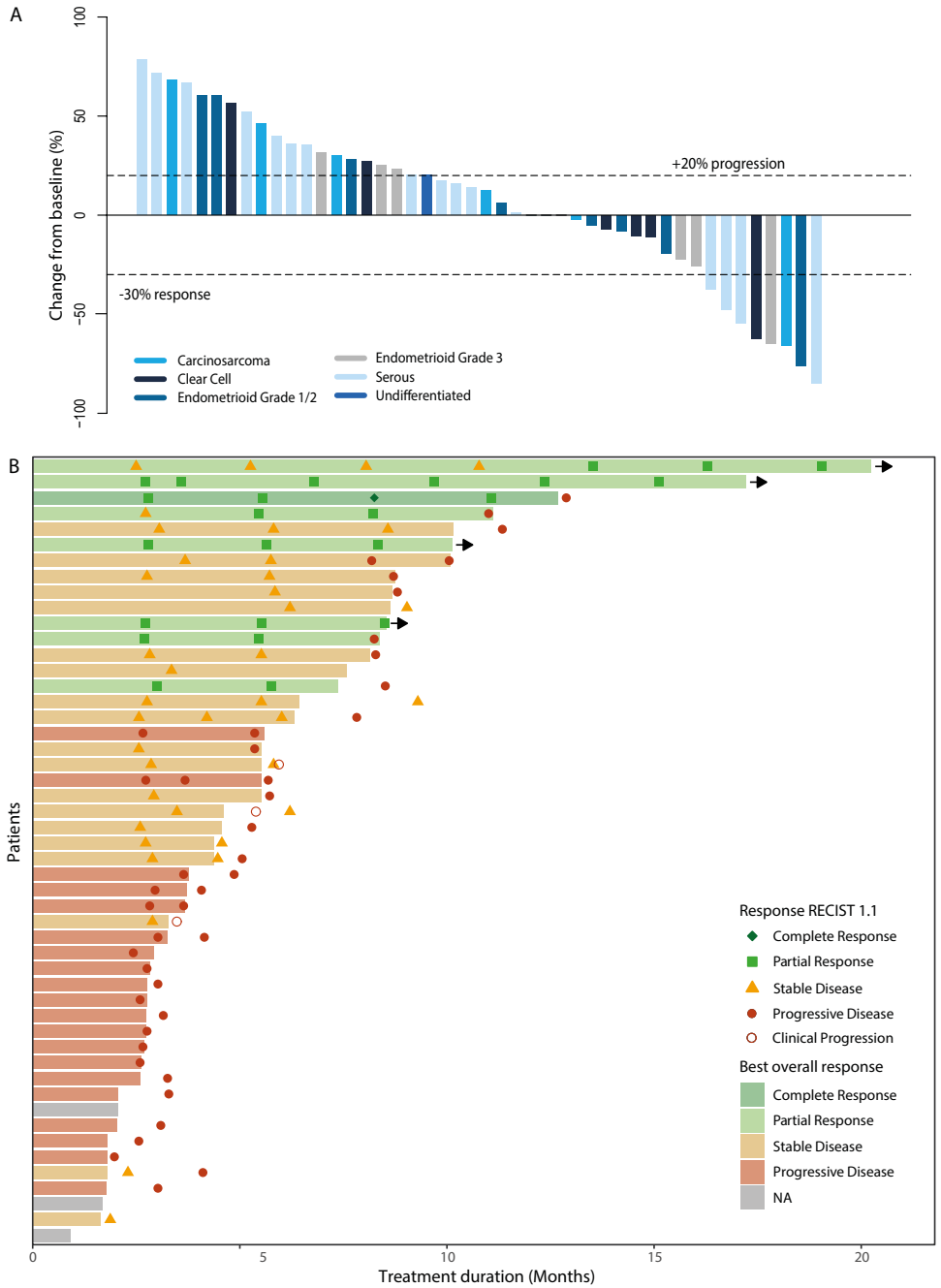

Figure 3. Best percentage change from baseline in sum of diameters of target lesions stratified by histology (A), and time on treatment with best overall tumor response per patient (B).
Each bar represents one patient. The black arrows indicate patients that were still on treatment at time of data cut-off. Each symbol represents a CT-scan with response according to RECIST v1.1

Table 2. Best overall response as per RECIST version 1.1 and progression-free survival estimate

Evaluable patients	***N* = 50**		
Best overall response, No. (%)		**Objective response**	
Complete Response	1 (2.0)	No. (%; 95% CI)	8 (16.0; 8.3 - 28.5)
Partial Response	7 (14.0)	Progression-free survival	
Stable Disease	19 (38.0)	6 m KM estimate, % (95% CI)	34.0 (23.1 - 50.0)
Progressive Disease	20 (40.0)	Median KM estimate, m (95% CI)	3.4 (2.8 - 6.2)
NA	3 (6.0)		

KM = Kaplan-Meier; NA = not available; m = months.

Safety

Of the evaluable patients, 44 (88%) had a treatment-related adverse event (TRAE) of any grade (Table 3). The most frequently reported (≥10%) TRAEs of any grade were fatigue (44%), nausea (38%), anemia (32%), diarrhea (26%), anorexia (24%), vomiting (16%), dysgeusia (16%), renal events (10%) and flu-like symptoms (10%). Grade 3 TRAEs occurred in 8 patients (16%), most frequently (10%) anemia. There were no grade 4 and 5 TRAEs.

One patient (2%) had to discontinue olaparib due to a treatment-related renal event and 12 patients (24%) had a dose reduction of olaparib due to TRAEs (1 patient with dose reduction to 100 mg, 2 to 150 mg, 7 to 200 mg and 2 to 250 mg BID). Three other patients (6%) had to interrupt olaparib due to TRAEs, but could resume treatment on the initial dose of 300 mg twice daily. One patient (2%) had to discontinue durvalumab early due to treatment-related diarrhea.

Table 3. Treatment-related adverse events

CTCAE term	**Any Grade**	**≥ Grade 2**	**Grade 3**
Any	44 (88)	28 (56)	8 (16)
Anemia	16 (32)	12 (24)	5 (10)
Fatigue	22 (44)	4 (8)	2 (4)
Renal events[a]	5 (10)	4 (8)	1 (2)
Nausea	19 (38)	3 (6)	1 (2)
Anorexia	12 (24)	3 (6)	1 (2)
Hepatotoxicity[b]	3 (6)	2 (4)	1 (2)
Leukopenia[c]	2 (4)	1 (2)	1 (2)
Infections[d]	4 (8)	4 (8)	0 (0)
Diarrhea	13 (26)	2 (4)	0 (0)
Vomiting	8 (16)	2 (4)	0 (0)
Flu like symptoms[e]	5 (10)	2 (4)	0 (0)
Abdominal pain[f]	3 (6)	2 (4)	0 (0)

Table 3. Treatment-related adverse events *(continued)*

CTCAE term	**Any Grade**	**≥ Grade 2**	**Grade 3**
Dysgeusia	8 (16)	1 (2)	0 (0)
Hypothyroidism	4 (8)	1 (2)	0 (0)
Edema limbs	2 (4)	1 (2)	0 (0)
Peripheral motor neuropathy	2 (4)	1 (2)	0 (0)
Hypertension	1 (2)	1 (2)	0 (0)
Gastrointestinal other[g]	6 (12)	0 (0)	0 (0)
Pain[h]	3 (6)	0 (0)	0 (0)
Respiratory disorders[i]	3 (6)	0 (0)	0 (0)
Dizziness	2 (4)	0 (0)	0 (0)
Dry skin	2 (4)	0 (0)	0 (0)
Pruritus[j]	2 (4)	0 (0)	0 (0)
Allergic reaction	1 (2)	0 (0)	0 (0)
Anosmia	1 (2)	0 (0)	0 (0)
Colitis	1 (2)	0 (0)	0 (0)
General disorders other	1 (2)	0 (0)	0 (0)
Hyperglycemia	1 (2)	0 (0)	0 (0)
Hypomagnesemia	1 (2)	0 (0)	0 (0)
Peripheral sensory neuropathy	1 (2)	0 (0)	0 (0)
Vaginal hemorrhage	1 (2)	0 (0)	0 (0)

NOTE. Adverse events graded according to the Common Terminology Criteria for Adverse Events (version 5.0). Data are reported as No. (%). The denominator to all calculated percentages is 50, the number of evaluable patients. No grade 4 or 5 treatment-related adverse events were reported.

a Renal event basket (including creatinine increased, acute kidney injury, chronic kidney disease)

b Hepatotoxicity basket (including alanine aminotransferase increased, aspartate aminotransferase increased and alkaline phosphatase increased)

c Leukopenia (including white blood cell and neutrophil count decreased)

d Infections (including eye, urinary tract, wound and pleural infections)

e Flu like symptoms basket (including predominantly fever, chills and flu like symptoms)

f Abdominal pain basket (including abdominal pain and stomach pain)

g Gastrointestinal other (including constipation, dry mouth, dysphagia, oral pain and salivary duct inflammation)

h Pain basket (including pain, facial pain and headache)

i Respiratory disorders basket (including cough and dyspnea)

j Pruritus basket (including pruritus and urticaria)

Discussion

The DOMEC trial is the first to report the efficacy and safety of combined immune-checkpoint inhibition and PARP inhibition for patients with metastatic, persistent or recurrent endometrial cancer including uterine carcinosarcoma. In this investigator-initiated phase 2 study, the combination of PD-L1 inhibitor durvalumab and PARP inhibitor olaparib did not meet the prespecified threshold of 50% 6-month PFS. The trial included a heterogeneous group of advanced endometrial cancers and PFS at 6 months was 34%. Nevertheless, some patients benefited with prolonged response and were still on treatment at the data cut-off date. The combined treatment was well tolerated without any grade 4 or 5 treatment-related adverse events and grade 3 in 16% of the patients.

Comparison with other studies that investigated new agents in advanced endometrial cancer is challenging due to the variety in study population and RECIST version used. Our study included patients with relatively unfavorable characteristics (e.g. worse WHO performance status, 80% high-grade endometrial cancer including 14% carcinosarcomas, 59% molecularly classified as p53abn, and 80% of NSMP endometrial cancers were ER-negative). Reported response rates of single-agent PD-(L)1 inhibitors strongly depend on MMR status in endometrial cancer. Studies investigating checkpoint inhibition in MMRd advanced endometrial cancer patients showed a median PFS of 4.4 to 25.7 months with ORR of 26.7 to 57.1%.[7, 9-11] These outcomes were better than those of the DOMEC trial, both in the MMRd subgroup and in our overall population. In the setting of immunotherapy, endometrial cancers classified as *POLE*mut, NSMP and p53abn are often referred to as MMR-proficient (MMRp). The response rates in our study seem to be better than those of studies with checkpoint inhibition monotherapy in MMRp endometrial cancer; Those studies report median PFS of 1.8 to 1.9 months and ORR of 3.0 to 13.4%, while reported rates of grade 3 or higher TRAEs were similar (13.5 to 19%).[9-12] The combination of pembrolizumab with the multitarget angiogenesis inhibitor lenvatinib, which has been approved by the FDA for advanced MMRp endometrial cancer, provided better outcomes irrespective of MMR status, with median PFS of 18.8 and 7.4 months and ORRs of 63.6 and 37.2% in MMRd and MMRp advanced endometrial cancer, respectively. However, more grade 3 or higher TRAEs (67%) were observed using this combination therapy.[5, 26]

The combination of durvalumab and olaparib was well tolerated. One patient had to discontinue olaparib and one patient had to discontinue durvalumab treatment due to TRAEs. Treatment modifications were made in 34% of the patients. The most common TRAEs of any grade were fatigue (44%), nausea (38%) and anemia (32%), and the most common grade 3 TRAE was anemia (10%). No olaparib-related adverse events of special interest (pneumonitis, myelodysplastic syndromes, or new primary malignancies) were reported. The most commonly reported durvalumab-related adverse events of special interest were diarrhea, renal events and hepatotoxicity. No new safety signals were observed, in line with those previously observed in respective combination and monotherapy studies.[10, 27-30]

The main strength of our study is that it is the first to report the efficacy and safety of combined immune-checkpoint inhibition and PARP inhibition for patients with metastatic or recurrent endometrial cancer. All tumors were molecularly classified.[23] This treatment combination has a rationale from preclinical and correlative data.[20] Although some molecular subgroups could be expected to benefit more than others, a synergistic effect could potentially occur in all types of advanced endometrial cancer. Therefore, an all-comer design was chosen. On the other hand, this study design introduced limitations. This study is limited by its heterogeneous patient, prior treatment and tumor characteristics. Due to the heterogeneity and the absence of a control group, it is difficult to put the clinical efficacy into perspective and draw any hard conclusions. In addition, the sample size was too small to perform powered subgroup analyses to make mature recommendations on patient selection for future clinical trials.

In order to generate recommendations on precision (combination) therapy, translational studies are needed to enhance knowledge on biomarkers. Given the good tolerance and suggestion of better performance than anti-PD(L)1 monotherapy in MMRp advanced endometrial cancer, the combination of durvalumab and olaparib might be of interest in a selected group of patients despite insufficient efficacy in the overall DOMEC population. Subgroups of interest might be the p53abn endometrial cancer, hormone receptor-negative NSMP endometrial cancer, and also MMRd tumors without durable response to checkpoint inhibition.[17, 20] Within the p53abn endometrial cancers, specifically, tumors with HRD are of interest. This was supported by a good response in 3 patients with p53abn endometrial cancer with known *BRCA 1* germline mutations. Another interesting finding was that one of the seven unfavorable p53abn carcinosarcomas had a durable response of >17 months, whereas she previously had only a short duration of disease control after primary treatment with surgery and chemotherapy. Additional exploratory analyses on *BRCA* mutational status, HRD and immunomonitoring is being planned, and will potentially set directions for future research. Further insight could be obtained from the currently recruiting phase 3 RUBY (NCT03981796) and DUO-E (NCT04269200) trials. These studies investigate the combination of platinum-based chemotherapy, checkpoint inhibitors and PARP inhibitors in the first-line treatment of advanced endometrial cancer. The *Trans*PORTEC consortium is initiating the RAINBO program in early-stage endometrial cancer, consisting of four academic trials for each of the four molecular subgroups.[31, 32] This approach should be extended to the advanced setting to identify the best molecularly

based systemic therapy for every patient with endometrial cancer.

In conclusion, the combination of checkpoint inhibitor durvalumab and PARP inhibitor olaparib was well tolerated in our group of patients with metastatic or recurrent endometrial cancer, but did not reach the 6-month PFS of 50%, and was therefore insufficient to recommend for a phase 3 trial in the overall patient population. However, with further knowledge on predictive biomarkers, this combination might be of interest in a selected group of patients with advanced endometrial cancer.

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APPENDIX A1. ELIGIBILITY CRITERIA

Inclusion criteria

1 Written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow-up assessments.
2 Age $\geq$ 18 years old
3 Histologically confirmed diagnosis of endometrial cancer or carcinosarcoma of the endometrium. Besides central revision, a tumor block or 20 slides are asked for TR.
4 Metastatic disease or locally advanced tumor not amenable to local therapy.
5 Documented progressive disease before enrolment.
6 Measurable lesions outside irradiated field *or* progressive measurable lesions in irradiated area
7 Not eligible for hormonal therapy (because of negative hormone receptor/poor differentiation, or after failure of hormonal therapy).
8 Previous failure of chemotherapy, or refusal to undergo chemotherapy or chemo-naive patients not suitable for chemotherapy.
9 WHO performance 0-1
10 Adequate organ system function as measured within 28 days prior to administration of study treatment, as defined below:
   - Hemoglobin ≥ 10.0 g/dL, with no blood transfusion in the past 28 days.
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - Platelet count ≥ 100 x 10^9/L
   - Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) (not applicable to Gilbert's syndrome)
   - Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x ULN unless liver metastases are present in which case they must be ≤ 5x ULN
   - Patients must have creatinine clearance estimated of ≥51 mL/min estimated using the Cockcroft-Gault equation or 24 hr urine clearance.
11 Expected adequacy of follow-up
12 Life expectancy of at least 16 weeks.
13 Measurable disease as defined by RECIST 1.1 criteria
14 Able to swallow and retain oral medication.
15 Body weight > 30 kg

Exclusion criteria

1 Participation in another clinical study with an investigational product during the last month or previous enrolment in the present study.
2 Any previous treatment with PARP inhibitor, including olaparib and/or any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab.
3 History of another primary malignancy that could conceivably be active evaluated by the study physician. Examples include, but are not limited to:
   - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence.
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   - Adequately treated carcinoma in situ without evidence of disease.

4 History of leptomeningeal carcinomatosis. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids (maximum 2 mg/day) before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.
5 Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome
6 Concomitant use of known strong CYP3A inhibitors (eg. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks.
7 Concomitant use of known strong (eg. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

8 Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
   - Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
   - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab and olaparib may be included only after consultation with the Study Physician.

9 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
10 Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
11 Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.
12 History of active primary immunodeficiency
13 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
   - Patients with vitiligo or alopecia
   - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
   - Any chronic skin condition that does not require systemic therapy
   - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
   - Patients with celiac disease controlled by diet alone

14 Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

15 Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
16 Patients with an expected or known hypersensitivity to olaparib or durvalumab or any of the excipients of the products.
17 Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).
18 Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.
19 Female patients who are pregnant or breastfeeding or patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy.

Chapter 7

General discussion and future perspectives

7. GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Over the last decade, essential knowledge has been gained on the molecular basis of endometrial cancer development and behavior. This has led to the integration of a prognostic model based on four molecular subgroups and histopathological factors, including stage, depth of myometrial invasion, histopathologic type, Federation of Gynecology and Obstetrics (FIGO) grade, and lymphovascular space invasion (LVSI). Most patients present with early-stage low risk or intermediate-risk endometrial cancers. However, about 15 to 20% of patients suffer from high risk disease, including early-stage grade 3 or non-endometrioid cancers, and more advanced stage of disease. The molecular classification, which has both prognostic and predictive value, is particularly relevant in the context of these high risk endometrial cancers, and might lead to treatment individualization and development of more effective and less toxic adjuvant treatments.

This thesis focused on treatment outcomes of high risk endometrial cancer and corresponding patients' and clinicians' preferences regarding adjuvant treatment decisions; molecular studies on the etiology of mismatch repair deficiency (MMRd) in intermediate and high risk endometrial cancer; and the combination of immunotherapy and PARP inhibition for the treatment of recurrent or metastatic endometrial cancer. In this chapter, the main findings and implications of these studies and future perspectives for innovative treatments and research are discussed and placed into perspective of current literature.

7.1. Adjuvant treatment for high risk endometrial cancer

Women with high risk endometrial cancer have been treated with pelvic radiotherapy for several decades. The PORTEC-3 trial compared adjuvant chemoradiotherapy versus radiotherapy alone for women with high risk endometrial cancer and showed a 5-year overall survival benefit of 5% (81% versus 76%) and failure-free survival benefit of 7% (76% versus 69%) with chemoradiotherapy.[1] Better insight into which patients are likely to benefit from adding adjuvant chemotherapy is essential to facilitate treatment decisions. The greatest overall survival benefit of more than 10% was found for women with serous cancers and those with stage III disease.[1] Translational research in the PORTEC-3 trial showed that p53 abnormal (p53abn) endometrial cancers have a highly significant benefit from chemoradiotherapy with an absolute 5-year overall survival benefit of 23% (65% versus 42%). Patients with no specific molecular profile (NSMP) endometrial cancers seemed to benefit from chemoradiotherapy in terms of 5-year recurrence-free survival (80% versus 68%, but not statistically significant due to the small sample size), while for MMRd endometrial cancers, no benefit was found (68% with chemoradiotherapy versus 76% with radiotherapy alone, not statistically significant). Those with *POLE* mutant (*POLE*mut) cancers had an excellent prognosis irrespective of adjuvant treatment modality.[2]

In addition to the overall survival and progression-free survival benefit of adding adjuvant chemotherapy to pelvic radiotherapy, it is important to consider the negative treatment effects. Therefore, long-term toxicity and health-related quality of life in the PORTEC-3 trial and their influence on treatment decisions were investigated in **chapter 2** and **chapter 3** of this thesis, respectively, and discussed in the next paragraph.

Long-term toxicity and health-related quality of life

Adjuvant treatment is associated with additional morbidity in comparison to surgery alone. In the PORTEC-2[3] and PORTEC-3 trial (reported in **chapter 2**), a significant proportion of patients treated with external beam pelvic radiotherapy experienced long-term urinary and gastrointestinal symptoms, such as urinary frequency (23 to 31%), diarrhea and fecal leakage (8 to 15%). These long-term symptoms may have an impact on physical and role functioning of the cancer survivors.[3,4] In the PORTEC-2 and -3 trials, the majority of patients were treated with 3-dimensional conformal radiotherapy (3DCRT). Current radiotherapy techniques such as intensity modulated radiotherapy (IMRT) and volumetric modulated arc radiotherapy (VMAT; Figure 1) have shown to reduce the risk of treatment-related acute and late adverse events in women undergoing pelvic radiotherapy in randomized studies.[5-9] In an analysis of the radiotherapy techniques used in the PORTEC-3 trial, in which about 15% of patients were treated with IMRT, gastrointestinal and hematological toxicity were reduced with IMRT compared to 3DCRT. Thus, toxicity rates in current clinical practice are expected to be lower than in previous studies.[5]

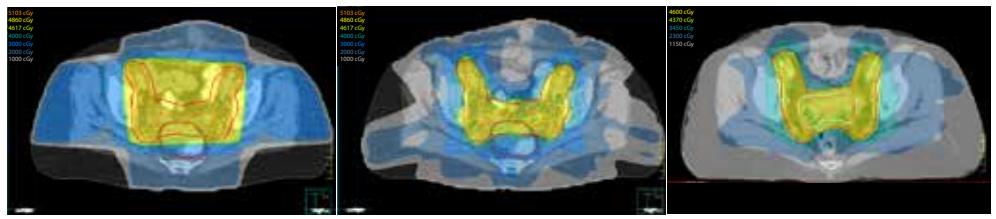

Figure 1. Examples of dose distributions of pelvic external beam radiotherapy for three different radiation techniques (A) 3-dimensional conformal radiotherapy, (B) intensity modulated radiotherapy and (C) volumetric modulated arc therapy.

Intensifying treatment with the addition of adjuvant chemotherapy to radiotherapy has a significant impact on the toxicity profile, with more frequent and severe (grade 3 to 4) adverse events and impaired health-related quality of life (HRQOL) during and shortly after treatment in the PORTEC-3 trial. The most important persisting toxicity was grade 2 sensory neuropathy.[10] In our long-term analysis of adverse events and HRQOL in the PORTEC-3 trial, we showed that recovery from grade 2 neuropathy was greatest in the first months after completion of chemotherapy and continued to improve during 2 years of follow-up. Thereafter, grade 2 sensory neuropathy remained constant up to 5 years after treatment in about 6% of patients treated with chemoradiotherapy versus 0% of patients treated with radiotherapy alone. Correspondingly, 24% of the patients who received chemoradiotherapy reported "quite a bit" or "very much" tingling or numbness in hands and/or feet on the quality of life questionnaires at 5 years, compared to 9% among patients treated with adjuvant radiotherapy alone. Concerning physical and role functioning, and weakness in the extremities, we found a statistically significant and clinically relevant negative impact up to 3 years after chemoradiotherapy. Thereafter, scores were similar to the radiotherapy alone group.

The rate of reported long-term tingling or numbness in the PORTEC-3 trial is in line with rates reported in the GOG-258 trial. Both in the GOG-258 combined chemoradiotherapy arm (using the same schedule as PORTEC-3) and the chemotherapy alone arm, "quite a bit" or "very much" tingling or numbness in hands and/or feet were reported by 30% of the patients at 5 years, while baseline rates were less than 5% and the highest rates of 41% to 44% were seen at 18 weeks after treatment.[11] The levels and the pattern of recovery of patient-reported tingling or numbness in studies of first-line therapy with carboplatin and paclitaxel in ovarian cancer were comparable to the PORTEC-3 trial results.[12, 13] The randomized GOG-249 trial also showed significantly higher chemotherapy-induced peripheral neuropathy rates in the combined brachytherapy and chemotherapy arm. Even while patients only received 3 cycles of carboplatin and paclitaxel, the rate of sensory neuropathy grade 2 was similar with 10% at 2 years.[14] Overall, patient-reported significant tingling or numbness persists in about 24 to 30% of patients after carboplatin and paclitaxel chemotherapy.

The contemporary challenge is to avoid significant neuropathy symptoms caused by adjuvant chemotherapy which have a long-lasting impact on the patient's functioning and quality of life. Unfortunately, no effective prevention strategy against sensory neuropathy currently exists.[15, 16] Data on risk factors for developing chemotherapy-induced sensory neuropathy are inconsistent,[17] and no significant factors were identified in our study. The incidence of peripheral neuropathy increases with age, at the same time as the prevalence of systemic disorders like diabetes mellitus and 'ageing' of the peripheral nervous system.

In our study, more deterioration of global health/QOL and symptoms of pain, fatigue and tingling or numbness was seen among patients aged 70 years or older than among younger patients. This observation was more pronounced after chemoradiotherapy compared to radiotherapy alone, suggesting a synergistic effect. Hence, older patients seem to be more susceptible to long-term impairment from intensified adjuvant therapy. On the other hand, efficacy of chemoradiotherapy is at least equivalent or even superior in older patients compared to younger patients. This should be considered during patient counseling.

Treatment preferences

The results presented in **chapter 3** give more insight into how survival benefit and the adverse events of chemoradiotherapy balance out for patients and clinicians, and which factors influence the treatment decision. We found that patients desired higher survival benefits to prefer adjuvant chemoradiotherapy over radiotherapy alone than clinicians. Patients reported a minimal threshold of 10% survival benefit (median) over the baseline 5-year survival rate of 75% to make adjuvant chemoradiotherapy worthwhile, while for clinicians this threshold was 5%.

Our results are in contrast to the patient preference study related to the PORTEC-3 trial conducted by the Australia New Zealand Gynecological Oncology Group (ANZGOG). In this sub-study among 83 patients with high risk endometrial cancer recruited to the PORTEC-3 trial, patients desired lower benefits than clinicians to make chemoradiotherapy worthwhile (4% versus 10% improvement over a 5-year survival rate of 65%).[18] For clinicians, this difference may be explained by their clinical experience with chemotherapy, and knowledge of the Dutch clinicians of the PORTEC-3 trial results in contrast to those in the ANZGOG. For patients, the relatively low required survival benefit in the ANZGOG sub-study may be explained by the selection of PORTEC-3 participants who were likely to accept chemotherapy for an uncertain benefit. Meanwhile, patient preferences in our study were clearly influenced by treatment history, and most patients (75%) did not receive chemotherapy. This was also a limitation of our study that could have been reinforced by the selection of patients who did not experience a recurrence, and thus are likely to be more satisfied with their treatment.[19] In line with our study, others have reported that patients who are about to undergo treatment or have experienced a treatment generally adapt to their decision by having a stronger preference for that treatment.[20-22]

Which factors influence treatment preferences?

Most published studies report high variability in patient preferences without identification of predictors.[18, 20, 23] We found a considerable variation in minimally desired survival benefit among both patients and clinicians. The range among clinicians was slightly narrower

than among patients. For patients, predictors for chemoradiotherapy preference were younger age, having no comorbidity and better numeracy skills. Nevertheless, individual treatment preferences are challenging to predict from baseline characteristics, and are likely influenced by a complex of experiences, values and attitudes. Participants, both patients and clinicians, considered the survival benefit the most important attribute in decision making, followed by the risk of developing long-term symptoms (i.e. neuropathy and impaired physical functioning). The importance of survival benefit is pronounced in preference studies among several types of cancer.[24, 25] Some studies emphasized the importance of quality of life in general as well.[25, 26]

Weighing the survival benefit in context of the molecular subgroups

Expected survival benefit should be considered when formulating recommendations on adjuvant treatment. With the actual 5% overall survival difference reported for the overall PORTEC-3 trial population,[1] only 40% of the patients and 63% of clinicians would prefer adjuvant chemoradiotherapy over radiotherapy alone. Based on an overall survival benefit of 10% for stage III disease,[1] 57% of the patients—still far from 100%—and 84% of the clinicians would prefer adjuvant chemoradiotherapy. The translational work of the PORTEC-3 trial suggested that this benefit in stage III is predominantly caused by the p53abn and NSMP cancers.[2] The preference for chemoradiotherapy increases to 75% and more than 90% for patients and clinicians, respectively, in case of a 20% benefit as observed in serous or p53abn endometrial cancer. However, the actual baseline survival rate for serous or p53abn cancers is lower than the 75% survival rate used in our study. The baseline survival rate of 50% used in the ANZGOG sub-study[18] is more appropriate. In this study, preference for chemoradiotherapy in case of a 20% benefit was even stronger. Considering these results, chemoradiotherapy can be recommended by the clinician for patients with serous or p53abn endometrial cancer who are fit enough to undergo treatment.

The results of our preference study cannot be directly applied to the NSMP subgroup. No statistically significant benefit in recurrence-free and overall survival was found in the NSMP subgroup of the PORTEC-3 trial. Estimates of 5-year survival are imprecise due to the small number of patients, although a trend was found with a similar magnitude of benefit as the overall trial results.[2] In essence, high risk NSMP endometrial cancer, especially ER/PR-negative and high grade tumors, may benefit from adjuvant chemoradiotherapy in terms of recurrence-free survival, although to a smaller extent as the p53abn group.[2] Due to the uncertainty of treatment benefit for patients with NSMP high risk endometrial cancer, shared decision making is essential for these patients.

Shared decision making

While we elucidated the potential survival benefit, negative treatment effects, and preferences in decision making in the previous sections, the question how to facilitate decision making remains challenging. The knowledge gained from **chapters 2 and 3** can facilitate (shared) decision making for adjuvant treatment for high risk endometrial cancer. Clinicians should be aware of the variability of preferences among endometrial cancer patients facing the treatment decision between adjuvant chemoradiotherapy and pelvic radiotherapy alone, and of the differences between clinicians and patients. Patients should be well informed by clinicians on the potential benefits and harms to facilitate a decision that is in line with the patient's personal values, attitudes and priorities. Impairments to be discussed are not limited to expected chemotherapy induced acute toxicity, but include toxicity due to standard adjuvant pelvic radiotherapy, even if the risk is equal in both arms (e.g. 36% risk of acute diarrhea). In addition, especially the risk estimate on long-term symptoms should be discussed with each individual patient.

Sensory neuropathy is the most clinically relevant and bothersome persisting symptom among women treated with chemotherapy. Patient's hobbies and other social activities that might be impacted by neuropathy should be considered during shared decision making. Giving personalized practical examples can make the term 'sensory neuropathy' more conceivable since patients may not realize the impact of this adverse event, and terms like 'tingling', 'numbness' or 'neuropathy' might be abstract for patients without knowledge or experience. Moreover, it may be helpful to explore the patient's associations with the treatments considered—e.g. experiences from close family members—and discuss the potential bias this may cause.

Providing relevant information and noting the patient's medical history is essential for shared decision making. However, the information can be biased since clinicians may underestimate patients' preferences for less toxic treatments.[27, 28] The aspects discussed above could be implemented in a pre-consultation online decision aid to provide unbiased information and help the patient to clarify personal values and identify their preferences. It may help to align consultation and shared decision making to the issues that matter most to the patient.

Future perspectives

The molecular classification of endometrial cancer will be the basis for inclusion criteria of future clinical trials and treatment recommendations. The four molecular subgroups have distinct prognostic and predictive characteristics, and thus different recommendations can be made for each group.

*POLE*mut high risk endometrial cancer

For high risk endometrial cancer with a pathogenic *POLE* mutation, treatment de-escalation should be strongly considered. Recurrence rates are extremely low, and salvage rates in case of recurrence are high.[29] Given the favorable outcomes of *POLE*mut endometrial cancer, omitting adjuvant treatment is likely safe in *POLE*mut early-stage endometrial cancer, and is currently being investigated. The PORTEC-4a trial and TAPER trial are two prospective clinical trials including stage I-II *POLE*mut cases that do not receive adjuvant treatment. Accrual of participants in the PORTEC-4a trial has been completed, and results are awaited. The question remains whether adjuvant treatment should also be de-escalated in (the rare scenario of) stage III *POLE*mut endometrial cancer. The single arm phase II RAINBO *POLE*mut-BLUE study will include stage I to III endometrial cancers to investigate whether adjuvant treatment can indeed be safely de-escalated or omitted. Another challenge to overcome is the limited availability of *POLE*mut testing; currently performed analysis to identify pathogenic *POLE* mutations is expensive and only available in academic medical centers of industrialized countries. In order to overcome this problem, more affordable and rapid assays to detect pathogenic *POLE* variants are being developed.[30]

p53abn high risk endometrial cancer

As mentioned above, p53abn endometrial cancers benefit most from adjuvant chemoradiotherapy compared to radiotherapy alone. However, their prognosis remains relatively poor, and further refinement of adjuvant treatment is warranted to improve outcomes for these patients. As explained in **chapter 5**, Poly (ADP-ribose) polymerase (PARP) inhibitors may be of additional value in the treatment of p53abn endometrial cancers, particularly in those that are homologous recombination deficient (HRD). This applies not only to the metastatic setting, but possibly also to the adjuvant setting. PARP inhibition would be of interest in future clinical trials for high risk p53abn endometrial cancer. For example in the RAINBO p53abn-RED trial, in which patients with stage I-III p53abn endometrial cancer will be randomized between concurrent chemoradiotherapy and chemoradiotherapy plus olaparib.

Another targeted agent of interest for p53abn endometrial cancer is Her2 blockade since 20-25% of the serous or p53abn cancers have overexpression or amplification of Her2Neu.[31] In a phase 2 trial, this combination improved progression-free survival compared to chemotherapy alone for advanced endometrial cancer.[32] A three-arm randomized trial comparing adjuvant chemotherapy alone versus chemotherapy with trastuzumab or with trastuzumab and pertuzumab in the adjuvant setting is being initiated by the NRG group with NCI in the United States together with the Canadian and Australian groups.

NSMP high risk endometrial cancer

The NSMP group is a heterogeneous group, dominated by endometrioid endometrial cancers, with generally an intermediate prognosis. Currently, histopathological factors such as stage, grade, LVSI, and histologic type remain most important for prognostication. Further refinement of predictive biomarkers is warranted within this molecular group. The majority of high risk NSMP tumors are hormone receptor positive (88%), with a significantly more favorable prognosis than those with negative hormone receptor status.[33] In estrogen receptor (ER)-positive NSMP tumors, adjuvant hormonal therapy after pelvic radiotherapy may be preferable to chemotherapy in view of the more favorable toxicity profile. No survival benefit was found in previous studies using adjuvant hormonal therapy; however, these studies included a heterogeneous patient population without selecting for histology, molecular subtype and receptor status.[34] Most of the participants had low and intermediate risk disease with only 3 trials including patients with higher risk disease.

In the RAINBO NSMP-ORANGE trial, patients with ER-positive stage II (with substantial LVSI) or stage III endometrial cancer will be randomized between adjuvant pelvic radiotherapy plus hormonal treatment and chemoradiotherapy, aiming for less toxicity and better quality of life with at least similar recurrence-free survival. The recurrence-free survival benefit of chemotherapy seems to be less pronounced in these cases than in ER-negative NSMP endometrial cancers.[33] Therefore the control arm can be challenged, especially since chemotherapy might deter patients from participating in the trial.

Whereas NSMP tumors have an intermediate prognosis in the overall endometrial cancer population, high risk grade 3 NSMP endometrial cancers have an unfavorable prognosis,[35] possibly due to a more significant proportion of hormone receptor negative cases and L1CAM overexpression. For hormone receptor negative NSMP tumors, targeted agents should be investigated. Targets of interest may be 1q32.1 amplification by MDM4 inhibition[36], PI3K/AKT/mTOR signaling pathway, Wnt/β-catenin signaling pathway or L1CAM. In case of Her2-low endometrial cancer the combination of trastuzumab-deruxtecan might be of interest.[37]

MMRd high risk endometrial cancer

Within the MMRd high risk group, adjuvant chemotherapy seems to be less promising based on the PORTEC-3 trial results.[2] However, immunotherapy is of particular interest in this molecular subgroup. The efficacy of immunotherapy for MMRd endometrial cancer in the recurrent or metastatic setting will be discussed in *paragraph 7.3*. No trials have been published yet in the adjuvant setting, but several clinical trials are ongoing. The RAINBO MMRd-Green trial will include patients with stage II (with substantial LVSI) or stage III

MMRd endometrial cancer. Enrolled patients will be randomly assigned to receive adjuvant radiotherapy alone or radiotherapy combined with immunotherapy (durvalumab) during and after radiotherapy.

Health related quality of life

HRQOL remains of high importance in future studies, including the RAINBO program. De-escalation of adjuvant treatment within the POLE-BLUE trial is expected to improve HRQOL, as well as the replacement of chemotherapy by hormonal therapy in the NSMP-ORANGE trial. In **chapter 6**, the combination of PARP inhibition and immunotherapy seemed tolerable in the advanced setting. These two agents are expected to be tolerable as well in combination with chemoradiotherapy or pelvic radiotherapy in the adjuvant setting of the p53abn-RED and MMRd-Green trials, respectively. Since all trials will use the EORTC QLQ-C30 and the EN-24 module for assessment of HRQOL, an overall comparison for the whole RAINBO cohort treated with molecular group based targeted treatment can be made eventually.

It remains a challenge to measure the clinical relevance of statistically significant differences in HRQOL scores. Mean differences of 10 points or more are widely considered clinically meaningful when interpreting EORTC QLQ-C30 scales in clinical trials.[38, 39] However, it is plausible that minimally important differences vary by scale, direction of change (improvement/deterioration) and clinical setting. The differences found within the trials could be placed into perspective by comparison of the four adjuvant treatment combinations with adjuvant radiotherapy alone and no adjuvant treatment. The quality of life analysis will also provide more insight into the toxicity of modern radiotherapy techniques combined with these new agents.

7.2. MMRd and Lynch syndrome

Further refinement of the MMRd molecular group

In **chapter 4** the etiology of MMRd endometrial cancer was further elucidated. The majority of MMRd endometrial cancers, 72% in the large combined cohort of PORTEC-1, -2 and -3, were caused by *MLH1* hypermethylation. Lynch syndrome was detected in 9.5% of the MMRd cases. Of the remaining 18%, most could be explained by a sporadic origin with detectable double somatic alterations.

Reported outcomes of MMRd endometrial cancers are predominantly driven by the *MLH1* hypermethylated cases, given the relatively low incidence of Lynch syndrome. Patients with non-methylated MMRd endometrial cancer seem to have a favorable prognosis compared to those with tumors caused by *MLH1* hypermethylation. Their favorable

prognosis has been assumed to be induced by the active local immune response with high rates of tumor infiltrating lymphocytes (TILs).[40, 41] The literature on survival differences among the MMRd subgroups is limited, but the trend we found towards worse prognosis of *MLH1* hypermethylated compared to non-methylated MMRd endometrial cancer was also seen in a Canadian study including 144 MMRd endometrioid endometrial cancers.[42] In addition, etiology seems to be a predictive factor as shown by a small phase 2 trial, where a significant improvements in 3-year progression-free survival (30% vs 100%; p = .017) and overall survival (43% vs 100%; p = .043) were found with pembrolizumab in 18 patients with methylated versus 6 patients with non-methylated recurrent endometrial cancer, respectively.[43] The differences in immunologic features and recurrence-free survival among MMRd cancers are essential to take into account in future research. Future clinical trials among MMRd endometrial cancer should be conducted with preplanned subgroup analysis based on etiology or other prognostic factors, such as features of the tumor-immunologic landscape. Further refinement of the MMRd subgroup will likely be of additional value for future treatment recommendations.

A relatively new potential prognostic and predictive factor within the MMRd subgroup is the presence of mature tertiary lymphoid structures (TLS). TLS can develop in non-lymphoid tissue with persistent inflammation. An association between non-methylated MMRd and TLS is presumable, especially in those with Lynch syndrome, since these patients have a strong immune activation due to continuously emerging premalignant lesions. Research among the high risk endometrial cancer patients of the PORTEC-3 trial showed mature TLS in 19% of the cases, and in 23% of the MMRd subgroup. Among MMRd endometrial cancers with non-methylated etiology or secondary p53-abnormality, TLS were significantly more common. Mature TLS were found to have significant favorable prognostic value in MMRd endometrial cancers of the PORTEC-3 trial.[44] However, the prognostic value of TLS was not demonstrated within the MMRd endometrial cancer subgroup of the pan-cancer analysis.[45]

Overall, data on TLS in endometrial cancer is limited, their prognostic and predictive value, and correlation with Lynch syndrome should be further investigated. L1CAM staining is an accessible and efficient method to identify mature TLS. If the hypothesized correlation between mature TLS and Lynch is strong enough to predict which non-methylated MMRd endometrial cancers are at higher risk or not at risk of having Lynch syndrome. L1CAM staining would be a valuable addition to the tumor screening for Lynch syndrome.

Universal tumor screening for Lynch syndrome

MMR-immunohistochemistry (IHC) of the four MMR proteins is recommended for the standard endometrial cancer work-up by the current guidelines.[46] MMR-IHC is not only important for its prognostic and predictive value, but also for its role in Lynch syndrome detection. A two-antibody (PMS2 and MSH6) approach could be considered a reliable alternative to improve cost-effectiveness.[47] Low-threshold additional MSH2- or MLH1-IHC in case of any doubt or inconclusive staining is still required. The addition of *MLH1* methylation analysis to MMR-IHC is an effective tumor-based triage method to identify patients suspected of Lynch syndrome; patients with tumors presenting a loss of MSH2 and/or MSH6, isolated loss of PMS2, or loss of MLH1 without *MLH1* hypermethylation are suspected of Lynch syndrome. This screening method has been adopted widely for colorectal cancer. For endometrial cancer, the tumor-based triage is a more effective strategy to identify Lynch syndrome families than age- and family history-based triage, since most endometrial cancer patients with Lynch syndrome do not meet clinical Lynch syndrome criteria. Our data support the recommendation to screen all patients with endometrial cancer for Lynch syndrome, irrespective of age. Based on the PORTEC-1, 2 and -3 data presented in **chapter 4,** among patients with suspected Lynch syndrome younger than 50 years, 50% were eventually diagnosed with Lynch syndrome. Among patients aged older than 50 years with tumors suspected of Lynch syndrome, about 34% were eventually diagnosed with Lynch syndrome. Nevertheless, the proportion of MMRd endometrial cancer caused by *MLH1* hypermethylation increases strongly with age. The lower prevalence of Lynch syndrome diagnoses with increasing age has been used as an argument to support an upper age screening limit. However, it is important to consider that most patients with endometrial cancer are diagnosed at an older age, with peak incidence between 65 and 80 years. This results in a rather high number of Lynch syndrome diagnoses in women aged 70 years or older, 17% in our cohort, while these diagnoses would be missed when an age limit was used.

Despite the fact that women presenting with endometrial cancer as their sentinel Lynch Syndrome cancer may be older than those presenting with colorectal cancer, these women might benefit from cancer surveillance since the risk of developing a second LS-associated cancer is still increased. Another argument supporting the tumor-based triage is the relatively high frequency of *MSH6* germline mutations found in our study. Families with *MSH6* germline mutations are not efficiently identified by current clinical criteria for Lynch syndrome[48] due to the older age of onset of colorectal cancer, incomplete penetrance, and a higher risk and later age of onset of endometrial cancer.[49-52] Moreover, screening for Lynch syndrome in endometrial cancer will have consequences for the patient's family. Cascade testing can identify affected relatives who can benefit from cancer surveillance and risk-reducing treatment. Finally, besides screening for Lynch syndrome, combined

MMR-IHC with *MLH1* hypermethylation assay is useful for further refinement of the MMRd group with prognostic and predictive value, as discussed above.

The next step is to improve the specificity of the tumor-based triage since with the current approach 2 out of 3 patients are still offered a referral to the clinical geneticist without eventually being diagnosed as having Lynch syndrome. In addition, uncertainty can persist for these patients with a non-methylated MMRd tumor without detected germline mutation, and their follow-up depends on the family history. For these patients, tumor sequencing can be essential as it can demonstrate a sporadic origin of the tumor. Ideally, this step should be added to the tumor-based triage for patients with suspected Lynch syndrome who do not meet clinical criteria for referral to the clinical geneticist.

Currently, no methods are available to distinguish Lynch syndrome associated tumors from sporadic non-methylated tumors when pathogenic variants are detected by next-generation sequencing of tumor tissue. Therefore, additional genetic testing of blood or normal tissue samples is required. A proportion of these patients will have Lynch syndrome. In some cases no pathogenic variants can be detected, implying an unknown sporadic cause or a germline mutation that is not detectable by currently used assays. Nevertheless, many tumors are likely to be explained by double somatic alterations, and patient are no longer suspected of having Lynch syndrome. Thus, the addition of combined tumor and normal tissue sequencing to the tumor-based triage can reduce referrals of patients suspected of having Lynch syndrome by up to 60%, as shown in Figure 2.

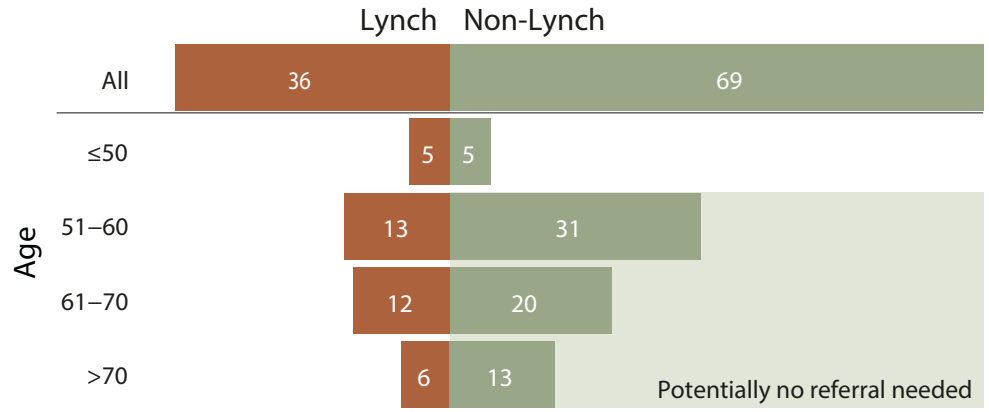

Figure 2. Distribution of Lynch syndrome suspected cases based on MMR-IHC and *MLH1*-hypermethylation assay. For patients aged 50 to 70 years with negative family history and those aged 70 years or older referral to a clinical geneticist could be omitted by identification of a somatic cause using sequencing of tumor and normal tissue.

7.3 Recurrent and metastatic endometrial cancer

In **chapter 5,** we discussed the urgent need for new treatment strategies and paradigms for patients with recurrent and metastatic endometrial cancer. Hormonal treatment is effective in up to 55% of the patients with advanced or recurrent low grade, ER-positive endometrial cancer.[53, 54] Potential further improvement of disease control rate at 24 weeks from 38% to 64% was demonstrated by the addition of palbociclib to letrozole in the phase 2 PALEO trial.[55] For all other patients with recurrent or metastatic endometrial cancer, prognosis is poor, and treatment options beyond first-line chemotherapy are scarce. Immunotherapy is being extensively explored, both as monotherapy and in combination with other targeted therapies, such as tyrosine kinase inhibitors, angiogenesis inhibitors and PARP inhibitors.

The first introduction of immunotherapy in clinical practice has been made by the accelerated US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval of pembrolizumab (2017 FDA) and dorstarlimab (2021 FDA and EMA) for the second-line systemic treatment of MMRd recurrent and metastatic endometrial after prior treatment with platinum-containing chemotherapy. For these patients, but also for patients with MMR proficient recurrent or metastatic endometrial cancer, FDA and EMA approved the combination of pembrolizumab and the antiangiogenic agent lenvatinib, a multiple receptor tyrosine kinase inhibitor targeting vascular endothelial growth factor receptors (VEGFRs) and fibroblast growth factor receptors (FGFRs).

Immunotherapy seems to be effective in MMRd advanced endometrial cancers, with reported objective response rates ranging between 27% and 57% and often durable responses.[56-60] The combination of pembrolizumab with lenvatinib has shown to be effective in both MMRd advanced endometrial cancer with an objective response rate of 64% and MMR proficient cases with an overall response rate of 37%. Grade 3 or higher treatment-related adverse events occurred in 67 to 89% of the patients, with dose reductions applied in 67%.[61, 62] Although highly effective, this treatment combination is significantly more toxic than immunotherapy alone or other treatment combinations. Therefore, immunotherapy alone is preferred in MMRd cases. Other treatment combinations, however, showed less promising (interim) survival results among patients with advanced or metastatic endometrial cancer, such as the combination of durvalumab plus olaparib (DOMEC-trial as described in **chapter 6**), carbozantinib plus nivolumab[63], and talazoparib plus avelumab[64]. An overview of published studies on immunotherapy alone or in combination with other target therapies in advanced endometrial cancer is displayed in Table 1.

Future perspectives

Although the reported response rates to immunotherapy are promising, these rates also implicate inefficacy in many patients (about 50 to 60%) with MMRd endometrial cancers. Further identification of predictive biomarkers within the MMRd endometrial cancer subgroup is warranted to optimize treatment recommendations. Causes of tumor development, such as Lynch syndrome, or immunological landscape features such as TILs, TLS, PD-L1 and Indoleamine 2, 3-dioxygenase 1 (IDO1) expression may predict response to immunotherapy. Especially for tumors not responding to immunotherapy, novel therapeutic targets and new molecules or strategies are needed.

The DOMEC study (**chapter 6**) helps to draw lessons for future research, although in retrospect the all-comer design can be challenged. The design was implemented because of the expected synergistic efficacy of combined durvalumab-olaparib. However, it is debatable whether the eligibility criteria should have been limited to the p53abn group. Molecular based inclusion criteria could have been used effortlessly since the molecular profile was often already analyzed in the clinical setting of recurrent or metastatic endometrial cancer. Stratification for homologous recombination deficiency (HRD) would be more challenging as it would require additional tests that are not yet fully established. As was already hypothesized beforehand, it was concluded that the treatment combination could be of special interest for the HRD p53abn advanced endometrial cancer population. The hypothesis is supported by preliminary results described in **chapter 6,** indicating that tumors with a *BRCA* germline mutation are likely to respond to combined olaparib-durvalumab.

Combining treatment modalities is not always better than monotherapy. Firstly, combined treatment generally worsens the toxicity profile and impacts the patient's quality of life. Secondly, the anticipated additional or synergistic effect of combination treatment based on preclinical trials is not always expressed *in vivo*. In **chapter 5,** we described the rationale for a synergistic effect of the combination of combined checkpoint inhibition and PARP inhibition, including activation of the cGAS/STING pathway and the innate immune response based on preclinical trials. However, efficacy could not be confirmed in **chapter 6** and other clinical trials.[66] Therefore, the hypothesis of a synergistic effect might be obsolete. By contrast, a recently published study generated the hypothesis that olaparib might reduce the effect of immunotherapy by an olaparib-mediated STAT3-activation suppressing antitumor immune response.[67, 68] STAT3-activation may also promote resistance to PARP inhibition. If this hypothesis can be confirmed in future studies, the STAT3 pathway might be a target of interest in combination with PARP inhibition.

Table 1. Published prospective trials investigating immunotherapy in advanced or recurrent endometrial cancer

Trial	Enrollment	Treatment	No. of patients	Prior chemotherapy lines	Low EEC	High EEC	Serous	CS	mPFS	ORR	mOS	TRAE any	TRAE ≥G3
Antill et al (PHAEDRA)[56]	2017-2018	Durvalumab	35 MMRd	0: 58%; 1: 39%; ≥2: 3%	72%	22%	0%	0%	8.3	47%	NR	93%	NR
			36 MMRp	0: 8%; 1: 63%; ≥2: 29%	26%	31%	31%	0%	1.8	3%	11.5		
Oaknin et al (GARNET)[57, 58]	2016-2019	Dostarlimab	103 MMRd	1: 63%; 2: 26%; ≥3: 11%	68%	4%	4%	0%	8.1*	45%	NR*	64%	14%
			142 MMRp	1: 46%; 2: 44%; ≥3: 11%	23%	5%	38%	1%	NR	13%	NR	72%	19%
Konstantinopoulos et al[59]	2016-2018	Avelumab	31	1: 29%; 2: 29%; ≥3: 42%		65%	10%	7%	NR	NR	NR	71%	19%**
			15 MMRd	*1: 40%; 2: 20%; ≥3: 40%*		*93%*	*0%*	*0%*	*4.4*	*27%*	*NR*	-	-
			16 MMRp	*1: 19%; 2: 37%; ≥3:44%*		*38%*	*19%*	*13%*	*1.9*	*6%*	*6.6*	-	-
O'Malley et al (KEYNOTE-158)[60]	2016-2020	Pembrolizumab	79 MSI-H	1: 48%; 2: 24%; ≥3: 28%	NR	NR	NR	NR	13.1	48%	NR	76%	12%
Ott et al (KEYNOTE-028)[65]	2014-2016	Pembrolizumab	24 PDL1+; 18/19 MSS	0: 8%; 1: 29%; 2: 21%; ≥3: 41%		71%	8%	4%	1.8	13%	NR	54%	16%
DOMEC (Chapter 6)	2019-2020	Durvalumab + olaparib	50	0: 16%; 1: 69%; 2: 26%; 3: 5%	20%	12%	36%	12%	3.3	16%	8.4	88%	16%**
			10 MMRd	*0: 30%; 1: 60%; 2: 10%*	*60%*	*30%*	*10%*	*0%*	*5.4*	*20%*	*7.5*	-	-
			40 MMRp	*0: 14%; 1: 58%; 2: 23%; 3: 5%*	*8%*	*8%*	*46%*	*18%*	*3.0*	*15%*	*10.5*	-	-
Makker et al (KEYNOTE-146)[62]	2015-2018	Lenvatinib + Pembrolizumab	108	1: 53%; 2: 37%; ≥3: 10%	29%	22%	32%	0%	7.4	40%	16.7	97%	67%
			11 MMRd	*1: 64%; 2: 27%; ≥3: 9%*	*55%*	*18%*	*0%*	*0%*	*18.8*	*64%*	*NR*	-	-
			94 MMRp	*1: 51%; 2: 38%; ≥3: 11%*	*27%*	*22%*	*35%*	*0%*	*7.4*	*37%*	*16.4*	-	-
Lheureux et al[63]	2018-2019	Cabozantinib + Nivolumab vs Nivolumab Mono	36 (2 MMRd) vs 18	≥3: 55%	NR	NR	NR	NR	5.3 vs 1.9	25% vs 17%	NR	NR	NR
		Cabozantinib + Nivolumab	9	NR	NR	NR	NR	100%	NR	11%	NR	NR	NR
Konstantinopoulos et al[64]	2016-2020	Talazoparib + Avelumab	35 MSS	NR	NR	NR	NR	NR	3.7	9%	NR	NR	NR
Makker et al (KEYNOTE-775)[61]	2018-2020	Lenvatinib + pembrolizumab vs TPC	411 vs 416	1: 76-79%; 2: 20-24%	13-14%	22-23%	25-28%	0%	7.2 vs 3.8	32% vs 15%	18.3 vs 11.4	100%	89% vs 73%
			346 vs 351 MMRp	*NR*	*NR*	*NR*	*NR*	*NR*	*6.6 vs 3.8*	*30% vs 15%*	*17.4 vs 12.0*	-	-

CS = carcinosarcoma; EEC = endometroid endometrial cancer; G3 = grade 3; High = high grade; Low = low grade; MMRd = mismatch repair deficient; MMRp = mismatch repair proficient; mOS = median overall survival; mPFS = median progression free survival; MSI-H = microsatellite instability-high; MSS = microsatellite stable; NR = not reported; ORR = objective response rate; PLD1+ = programmed death ligand-1 positive; TPC = physician's choice of doxorubicin or paclitaxel chemotherapy; TRAE = treatment related adverse events.

*JAMA (2020) publication, older data[58]

**No Grade 4 or 5 TRAEs

The answer to the question what interaction olaparib and durvalumab have in endometrial cancer *in vivo* is likely to be retrieved from the comparison of the immunotherapy arms of the 3-arm DUO-E and RUBY trials which included patients with recurrent or primary advanced endometrial cancer regardless of molecular group, with randomized allocation to chemotherapy with or without immunotherapy with or without PARP inhibition. Both studies have completed accrual, and results are awaited. Multiple phase 2 trials are currently planned or ongoing to investigate the efficacy of PARP inhibition in a serous or all-comer population (NCT03745950, NCT03617679, NCT04080284, NCT04716686). Subgroup analyses of the HRD tumors would be recommended to propose future trial designs. Molecularly driven trials, preferably with a basket or umbrella design, may identify new treatment strategies.

Uterine carcinosarcomas

Uterine carcinosarcomas are a rare gynecological malignancy, representing approximately 5% of all endometrial cancers. However, they account for 16% of all uterine cancer-related deaths.[69] Uterine carcinosarcomas can be defined as a biphasic tumor, characterized by both carcinomatous (epithelial) and sarcomatous (stromal tissue) elements, with aggressive clinical behavior. Molecular studies support that both elements originate from a carcinoma lineage that undergoes sarcomatous dedifferentiation. Therefore, uterine carcinosarcomas can be considered 'high risk histology' of endometrial cancer according to the WHO classification.

Historically, patients with uterine carcinosarcomas were excluded from endometrial cancer trials, but current insight into the molecular background supports including these patients, as was done in the DOMEC trial. The vast majority of uterine carcinosarcomas are p53abn.[70] MMRd has been reported in 6% to 30%, and it has been found to be a favorable prognostic factor.[70-72] *TP53* and *MMR* alterations are considered early events in carcinosarcoma development since they are majorly found in both tumor components.[71-73] Whereas uterine carcinosarcomas normally have an extremely poor prognosis, 1 out of 8 patients with a p53abn carcinosarcoma included in the DOMEC trial had a long and durable response of more than 2 years, whereas she had had a short duration of disease control after primary treatment with surgery and chemotherapy. This exceptional response indicates that selected patients could benefit from combined olaparib-durvalumab or as monotherapy. Factors to identify these patients, such as HRD related mutations, should be investigated in future research.

7.4 Conclusions

This thesis showed that adjuvant chemoradiotherapy can have a long-term impact on health-related quality of life of patients with high risk endometrial cancer. It is essential to incorporate the risk of long-lasting symptoms in treatment information to support and facilitate shared decision making. The individual patient's values and experiences should be explored to support a well-considered treatment decision. The importance of the molecular classification of endometrial cancer extends beyond its prognostic value and is known to have predictive value as well, and can be another cornerstone for treatment decisions in the adjuvant and metastatic setting. Therefore, incorporation of the molecular classification is essential in upcoming trials. For the MMRd, p53abn and NSMP subgroups, further refinement of the molecular classes is warranted to optimize individualized treatment. Combined MMR-IHC with *MLH1* hypermethylation assay-based triage can effectively identify the subset of patients with suspected Lynch syndrome, and is recommended for all patients diagnosed with endometrial cancer without age limit. The cause of MMRd could further refine the prognostification of the MMRd subgroup; their etiology is associated with the tumor's immunologic landscape and is likely to be predictive of immunotherapy response. Immunotherapy and targeted therapies are emerging, both in the adjuvant setting of high risk endometrial cancer and in the metastatic and recurrent setting. The combination of durvalumab and olaparib did not show sufficient efficacy in the all-comer metastatic endometrial cancer population of the DOMEC trial. However, this combination may be a treatment modality of interest for p53abn metastatic endometrial cancer with HRD. Future research into target therapy for recurrent and metastatic endometrial cancer is recommended to find new tolerable treatment options for these patients with an unfavorable prognosis.

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Appendices

Nederlandse samenvatting

List of publications and conference abstracts

Curriculum vitae

Dankwoord

NEDERLANDSE SAMENVATTING

Introductie

Endometriumcarcinoom (baarmoederkanker) is de meest voorkomende gynaecologische kanker in ontwikkelde landen. Endometriumcarcinoom komt het meest voor bij vrouwen van 60 tot 85 jaar. Vooral door vergrijzing en toename van obesitas is de incidentie de afgelopen decennia gestegen. De meerderheid van de vrouwen presenteert zich in een vroeg stadium, met het optreden van postmenopauzaal bloedverlies. Vanwege de vroege detectie is de prognose doorgaans goed. De standaard operatie bij vroeg stadium endometriumcarcinoom bestaat uit het operatief verwijderen van de baarmoeder, eileiders en eierstokken, meestal laparoscopisch ('kijkoperatie'). De adjuvante (aanvullende) behandeling hangt af van het risico op recidief.

Op basis van verschillende tumorkenmerken kan het recidief risico worden ingeschat; de belangrijke tumorkenmerken hiervoor zijn het stadium van ziekte, histologisch type, differentiatiegraad, diepte van ingroei in het myometrium, lymfangio-invasieve groei en de meer recent ontdekte specifieke moleculaire veranderingen. Er is de afgelopen decennia veel kennis vergaard over deze laatstgenoemde moleculaire veranderingen die leiden tot het ontstaan van verschillende typen endometriumcarcinoom. De basis werd gelegd door het moleculair-genetische onderzoek van 'The Cancer Genome Atlas' (TCGA) in 2013. Er werden vier moleculaire subgroepen van endometriumcarcinoom onderscheiden: (1) de groep gedreven door polymerase-epsilon (*POLE*)-mutatie met een goede prognose; (2) 'mismatch repair'-deficiënte groep (MMRd) veroorzaakt door een verandering in een van de mismatch repair-genen met een intermediaire prognose; (3) een 'copy number low'-groep zonder specifieke moleculaire kenmerken (NSMP) met een intermediaire prognose; en (4) de 'copy number high' of 'p53 abnormal' (p53abn) groep gedreven door een *TP53*-mutatie met een relatief slechte prognose.

Ongeveer 15 tot 20% van de vrouwen heeft een endometriumcarcinoom met hoog risico kenmerken. Dit betreft slecht gedifferentieerde tumoren in een vroeg stadium, tumoren met niet-endometrioïde histologie en tumoren met meer gevorderd ziektestadium. Binnen deze groep met hoog risico kenmerken is het moleculaire classificeren bijzonder relevant. Niet alleen voor het voorspellen van de recidiefkans, maar ook voor het individualiseren van de behandeling.

In de internationale PORTEC-3 studie werd voor 660 vrouwen met hoog risico endometriumcarcinoom de standaard adjuvante radiotherapie vergeleken met adjuvante radiotherapie gecombineerd met chemotherapie tijdens en na de

radiotherapie (chemoradiotherapie). Er werd een 5-jaars overlevingsvoordeel van 5% (76% versus 81%) en een verbetering van de 5-jaars recidief vrije overleving van 7% (69% versus 76%) gevonden met de gecombineerde chemoradiotherapie. De grootste overlevingswinst (van meer dan 10%) werd gevonden bij vrouwen met sereuze tumoren en bij stadium 3 ziekte. In het kader van de moleculaire classificatie toonde onderzoek op weefselmateriaal van deelnemers aan de PORTEC-3 studie dat vrouwen met p53abn endometriumcarcinoom een significant en klinisch relevant voordeel hadden van chemoradiotherapie, en leken patiënten met NSMP endometriumcarcinoom ook baat te hebben bij chemoradiotherapie. Voor MMRd endometriumcarcinomen werd echter geen voordeel gevonden van chemotherapie, en patiënten met een *POLE*-mutatie (*POLE*mut) hadden een uitstekende prognose, waarbij er geen verschil was tussen de twee adjuvante behandelingen.

Naast de voordelen van verbetering van de (recidief vrije en algehele) overleving zijn er ook negatieve effecten van adjuvante behandeling voor vrouwen met hoog risico endometriumcarcinoom, die hierna beschreven zullen worden.

Kwaliteit van leven en behandelkeuze

Voor elke individuele patiënte moet het mogelijke voordeel van de adjuvante behandeling worden afgewogen tegen de "kosten" in de zin van een langere behandelingsduur, toename van kans op nadelige effecten en de mogelijk negatieve invloed op de kwaliteit van leven op zowel de korte als lange termijn. Bijwerkingen zijn het meest frequent en ernstig tijdens de behandeling, maar sommige klachten kunnen blijvend zijn, en deze aanhoudende bijwerkingen mogen niet worden onderschat. Uitwendige radiotherapie van het bekken kan bijvoorbeeld gepaard gaan met bijwerkingen van de darmen en blaas. Ook op lange termijn kunnen sommige bijwerkingen aanhouden, zoals meer frequente aandrang voor ontlasting of lichte urine-incontinentie.

Het toevoegen van chemotherapie aan de uitwendige bestraling in de adjuvante behandeling van vrouwen met hoog risico endometriumcarcinoom blijkt een aanzienlijke invloed te hebben op het bijwerkingsprofiel. In **hoofdstuk 2** worden de kwaliteit van leven en toxiciteit in de PORTEC-3 studie tot 5 jaar na behandeling beschreven. Tijdens en kort na chemoradiotherapie traden er frequenter en meer ernstige bijwerkingen op dan bij radiotherapie alleen, met invloed op het lichamelijk en rol-gebonden functioneren van de patiënt. De meeste bijwerkingen verdwenen binnen het eerste jaar na behandeling. De belangrijkste aanhoudende bijwerking was sensorische perifere neuropathie. Dit werd door artsen bij 6% van de patiënten die behandeld waren met gecombineerde chemoradiotherapie gescoord als graad 2 bijwerking (invloed hebbend op dagelijkse

bezigheden), in vergelijking tot 0% na alleen radiotherapie. Sensorische neuropathie uit zich met name in tintelingen of gevoelloosheid in handen en/of voeten; 24% van de patiënten gaf in de kwaliteit van leven vragenlijst aan hier “nogal” of “heel erg” last van te hebben 5 jaar na behandeling met adjuvante chemoradiotherapie, vergeleken met 9% van de patiënten die alleen met adjuvante radiotherapie waren behandeld. In de eerste 3 jaar na chemoradiotherapie werd ook vaker een negatieve invloed op het fysieke en rol-gebonden functioneren gerapporteerd, en/of gevoel van zwakte in armen of benen; na 5 jaar waren de scores verbeterd en vergelijkbaar met die van de groep met alleen radiotherapie. De 5-jaars algemene gezondheid/kwaliteit van leven scores waren vergelijkbaar in beide onderzoeksgroepen.

De resultaten beschreven in **hoofdstuk 3** geven meer inzicht in hoe het overlevingsvoordeel en de bijwerkingen van chemoradiotherapie ten opzichte van radiotherapie alleen tegen elkaar opwegen vanuit het perspectief van patiënten behandeld voor hoog risico endometriumcarcinoom, en van hun behandelend artsen. Tevens werd onderzocht welke factoren de behandelkeuze beïnvloeden. Om adjuvante chemoradiotherapie te verkiezen boven radiotherapie hadden patiënten een hoger overlevingsvoordeel nodig dan artsen (mediaan 10% versus 5% overlevingsvoordeel). Echter, de variatie binnen de twee groepen was groot. Oudere patiënten en patiënten met comorbiditeit hadden een lagere voorkeur voor chemoradiotherapie, terwijl patiënten met betere rekenvaardigheden of een voorgeschiedenis met chemoradiotherapie een hogere voorkeur hadden voor chemoradiotherapie. Zowel patiënten als artsen vonden het overlevingsvoordeel het zwaarst wegen bij de besluitvorming. Dit werd gevolgd door de (blijvende) bijwerkingen op langere termijn.

MMRd en Lynch syndroom

Immunohistochemische kleuring van de MMR eiwitten kan, naast de bijdrage aan de moleculaire classificatie door de identificatie van MMRd tumoren, ook worden gebruikt als screeningmethode voor identificatie van patiënten die mogelijk het Lynch syndroom hebben. Lynch syndroom is een erfelijke aandoening met een afwijking in een van de MMR genen, waarbij er een verhoogde kans is op het ontwikkelen van darmkanker, endometriumcarcinoom en sommige andere kankersoorten. De meeste gevallen van MMRd-gerelateerd endometriumcarcinoom worden veroorzaakt door niet-erfelijke hypermethylering van de promoter van het *MLH1*-gen waardoor het gen zijn functie niet meer kan uitvoeren; slechts een klein deel wordt veroorzaakt door het Lynch syndroom. Het vaststellen van Lynch syndroom is van belang voor verdere behandelkeuzes en screening op (darm)kanker, zowel voor de patiënte zelf als voor haar familie.

In de studie beschreven in **hoofdstuk 4** wordt de oorzaak van MMRd-endometriumcarcinoom onderzocht in een groot, gecombineerd cohort van de PORTEC-1, -2 en -3 studies met in totaal 1336 patiënten met endometriumcarcinomen, waarvan 410 een MMRd tumor hadden. De meerderheid (72%) van deze MMRd-endometriumcarcinomen werd veroorzaakt door hypermethylering van de *MLH1*-promoter. Lynch syndroom werd vastgesteld in 9.5% van de MMRd tumoren, corresponderend met 3% van alle vrouwen met endometriumcarcinoom. Van de resterende 18.5% MMRd tumoren konden de meesten worden verklaard door een andere sporadische (niet erfelijke) oorsprong, door meerdere veranderingen in de tumor.

Alhoewel patiënten met endometriumcarcinoom veroorzaakt door Lynch syndroom over het algemeen jonger waren, was meer dan de helft ouder dan 60 jaar. Patiënten met endometriumcarcinoom veroorzaakt door het Lynch syndroom bleken doorgaans een betere ziektevrije overleving te hebben dan patiënten met endometriumcarcinoom veroorzaakt door *MLH1*-hypermethylatie (92% versus 79% bij 5 jaar), maar ook een hoger risico op het ontwikkelen van een tweede primaire maligniteit (12% versus 2% bij 10 jaar).

Gemetastaseerd of gerecidiveerd endometriumcarcinoom

De prognose voor gemetastaseerd of gerecidiveerd endometriumcarcinoom is slecht. Voor vrouwen met afstandsmetastasen van een endometriumcarcinoom bedraagt de 5-jaarsoverleving 10-20%. De eerstelijns systemische therapie bestaat uit platinum-bevattende chemotherapie of hormonale therapie. Er is geen standaard vervolgbehandeling. Moleculaire tumoreigenschappen zouden een aangrijpingspunt kunnen zijn voor een meer op de individuele tumor aangepaste behandeling. Zo heeft immuuntherapie goede effecten laten zien bij vrouwen met MMRd endometriumcarcinoom en kan dit al worden gebruikt voor de tweedelijns behandeling van MMRd gemetastaseerd of gerecidiveerd endometriumcarcinoom. Een andere meer specifieke doelgerichte behandeling is poly-(ADP-ribose) polymerase (PARP)-remming. PARP-remmers blokkeren een eiwit dat kankercellen gebruiken om DNA te herstellen. Uit preklinisch onderzoek is gebleken dat de combinatie van immuuntherapie en PARP-remming een versterkend effect kan hebben. In **hoofdstuk 5** wordt ingegaan op de moleculaire basis van deze middelen in de behandeling van gevorderd endometriumcarcinoom en wordt een overzicht gegeven van gepubliceerd, lopend en gepland klinisch onderzoek met deze middelen als mono- of combinatietherapie.

In **hoofdstuk 6** wordt de meer doelgerichte benadering in een klinische setting onderzocht en worden de resultaten van de DOMEC (‘Durvalumab and Olaparib in Metastatic/recurrent Endometrial Cancer’)-studie beschreven. De DOMEC-studie was

een Nederlands, prospectief, multicenter, fase 2 onderzoek naar de werkzaamheid van immuuntherapie door middel van de PD-L1-remmer durvalumab (elke vier weken 1.500 mg intraveneus) in combinatie met de PARP-remmer olaparib (tweemaal daags 300 mg tablet) bij 55 patiënten met gemetastaseerd of gerecidiveerd endometriumcarcinoom. Deze combinatiebehandeling werd goed verdragen, maar met een progressie vrije overleving na 6 maanden van 34% was de behandeling onvoldoende effectief om aan te bevelen voor een fase 3-studie in een vergelijkbare patiëntpopulatie. Desalniettemin vertoonden sommige patiënten een langdurige respons en werden zij op de sluitingsdatum van de studie na 2 jaar nog steeds behandeld. Er lijken dus patiënten te zijn die mogelijk wel baat hebben bij deze combinatiebehandeling, maar op dit moment is nog onvoldoende duidelijk welke biomarkers een goede respons op deze combinatie behandeling zouden kunnen voorspellen.

Discussie

In de discussie in **hoofdstuk 7** worden de belangrijkste bevindingen in het perspectief van bestaande literatuur geplaatst en worden implicaties voor de klinische praktijk en toekomstperspectief besproken. In dit proefschrift werd aangetoond dat adjuvante chemoradiotherapie op lange termijn nadelige gevolgen kan hebben voor patiënten met hoog risico endometriumcarcinoom, met name door perifere sensorische neuropathie. Het is essentieel om deze bevinding te bespreken in de afweging van voor- en nadelen van aanvullende chemotherapie. De waarden en ervaringen van de individuele patiënte zijn van belang om gezamenlijk tot een weloverwogen behandelbeslissing te komen.

Het belang van de moleculaire classificatie van endometriumcarcinoom reikt verder dan de prognostische waarde en kan tevens een basis zijn voor de beslissing over de beste behandeling, zowel in de adjuvante als gemetastaseerde setting. De integratie van de moleculaire classificatie in de dagelijkse praktijk en in toekomstige onderzoeken is daarom essentieel. Specifieke behandeling voor elke moleculaire groep is de basis voor het RAINBO umbrella programma, dat bestaat uit in totaal vier klinische onderzoeken met een gerichte onderzoeksvraag voor elke moleculaire subgroep. Het ultieme doel van toekomstig onderzoek is om voor elke patiënte een optimale balans te vinden tussen de effectiviteit van de behandeling en de bijkomende symptomen met de daarbij horende invloed op kwaliteit van leven. Voor de subgroepen MMRd, p53abn en NSMP is verdere verfijning van de moleculaire subgroepen gewenst om de behandeling in de toekomst nog verder te kunnen individualiseren.

Gecombineerde MMR-immunohistochemische kleuring en *MLH1*-hypermethylatie analyse kan effectief patiënten met vermoedelijk Lynch syndroom identificeren. Op basis van ons onderzoek wordt deze screening aanbevolen voor alle patiënten met de diagnose endometriumcarcinoom, ongeacht hun leeftijd. De moleculaire basis van MMRd heeft een prognostisch voorspellende waarde binnen de MMRd-subgroep en heeft daarnaast mogelijk voorspellende waarde voor de respons op immuuntherapie.

Immuuntherapie en gerichte therapieën zijn in opkomst, zowel in de adjuvante setting van hoog risico endometriumcarcinoom als in de gemetastaseerde setting. De combinatie van durvalumab en olaparib toonde onvoldoende werkzaamheid in de niet op moleculaire factoren geselecteerde groep patiënten met gemetastaseerd endometriumcarcinoom in de DOMEC-trial. Desalniettemin kan deze combinatie een interessante behandeling zijn voor vrouwen met p53abn endometriumcarcinoom met homologe recombinatie deficiëntie in de adjuvante of gemetastaseerde setting. Toekomstig onderzoek naar doelgerichte therapieën voor vrouwen met gemetastaseerd endometriumcarcinoom is noodzakelijk om nieuwe aanvaardbare behandelingsmogelijkheden te vinden voor deze patiënten met een ongunstige prognose.

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CURRICULUM VITAE

Cathalijne Catharina Bastiana Post werd op 13 september 1994 geboren te Nieuwegein. Na het behalen van haar VWO diploma (cum laude) aan College de Heemlanden te Houten, studeerde zij geneeskunde aan de Universiteit Utrecht. In augustus 2018 werd haar artsexamen behaald. Hierna was zij, in het verlengde van haar wetenschappelijke stage, gedurende drie maanden werkzaam als arts-onderzoeker bij de vakgroep Radiotherapie van het Universitair Medisch Centrum Utrecht. Gedurende deze periode heeft zij onder begeleiding van dr. J.J.C. Verhoeff een studieprotocol en subsidieaanvraag geschreven getiteld "Herbestraling van recidief gliomen: welk schema is het beste voor de patiënt". In juli 2019 werd de subsidie toegekend door KWF/Alpe d'Huzes.

Per 1 januari 2019 startte zij met promotieonderzoek naar de behandeling van endometriumcarcinoom bij de vakgroep Radiotherapie van het Leids Universitair Medische Centrum (LUMC) onder begeleiding van prof. dr. C.L. Creutzberg, dr. J.R. Kroep en dr. T. Bosse, en vanaf 1 februari 2021 startte Cathalijne daarnaast met de opleiding tot Radiotherapeut-Oncoloog (opleiders: prof. dr. C.L. Creutzberg en dr. I. Lips).

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