Towards personalized treatment for high risk endometrial cancer

Post, C.C.B.

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]

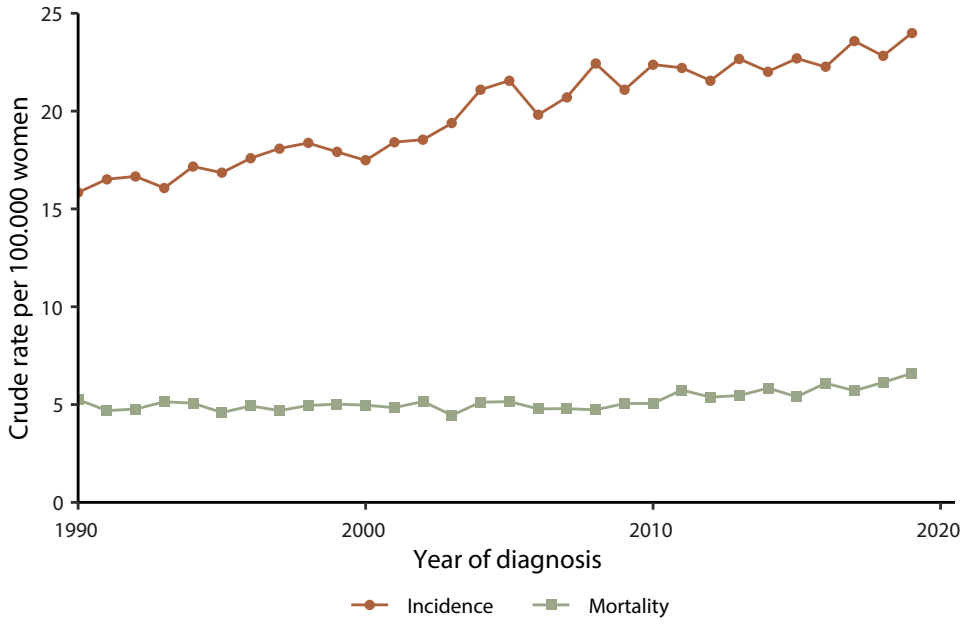

Figure 1. Netherlands Cancer Registry: Increasing crude incidence and mortality of endometrial cancer in the Netherlands between 1990 and 2019[2]

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].

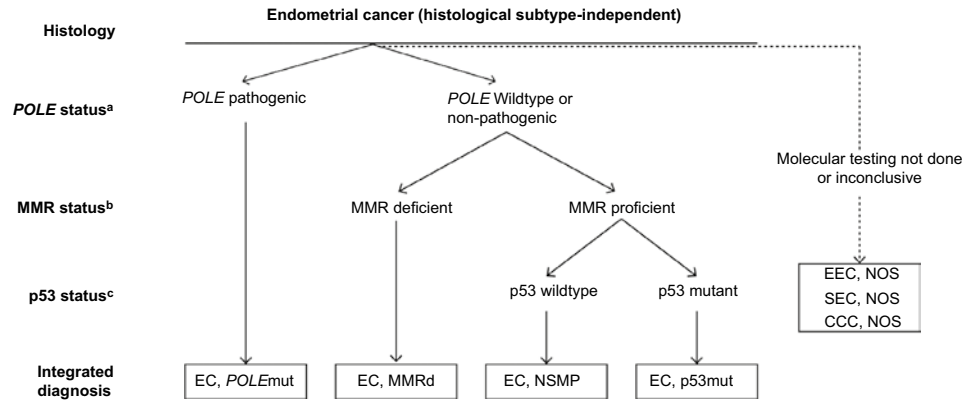

Figure 2. Diagnostic algorithm for the integrated histomolecular endometrial cancer classification[8]
EC = endometrial cancer; MMR = mismatch repair; MMRd = mismatch repair-deficient; NSMP = no specific molecular profile.
[a]Pathogenic *POLE* variants include p.Pro286Arg, p.Val411Leu, p.Ala456Pro, p.Ser459Phe 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.

References

1 Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. The Lancet. 2016;387(10023):1094-108.
2 IKNL. Dutch cancer figures [Cijfers over Kanker]. Available from: http://www.cijfersoverkanker.nl [Accessed 26 Apr 2022].
3 National Cancer Institute. Cancer Stat Facts: Uterine Cancer. Available from: https://seer.cancer.gov/statfacts/html/corp.html [Accessed 26 Apr 2022].
4 Levine DA, The Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497:67.
5 Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 2021;31(1):12-39.
6 Koskas M, Amant F, Mirza MR, Creutzberg CL. Cancer of the corpus uteri: 2021 update. Int J Gynaecol Obstet. 2021;155 Suppl 1:45-60.
7 Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10-7.
8 World Health Organisation Classification of Tumours Editorial Board. WHO classification of tumours female genital tumours. 5th ed. Herrington CS, editor. International Agency for Research on Cancer; 2020.
9 Peters EEM, Leon-Castillo A, Smit V, Boennelycke M, Hogdall E, Hogdall C, et al. Defining substantial lymphovascular space invasion in endometrial cancer. Int J Gynecol Pathol. 2022;41(3):220-6.
10 Peters EEM, Bartosch C, McCluggage WG, Genestie C, Lax SF, Nout R, et al. Reproducibility of lymphovascular space invasion (LVSI) assessment in endometrial cancer. Histopathology. 2019;75(1):128-36.
11 Jaishankar S, Pifer PM, Bhargava R, Keller A, Musunuru HB, Patel AK, et al. Is substantial lymphovascular space invasion prognostic for clinical outcomes in type II endometrial cancer? Clin Oncol (R Coll Radiol). 2022;34(7):452-458.
12 Briet JM, Hollema H, Reesink N, Aalders JG, Mourits MJ, ten Hoor KA, et al. Lymphvascular space involvement: an independent prognostic factor in endometrial cancer. Gynecol Oncol. 2005;96(3):799.
13 Stalberg K, Bjurberg M, Borgfeldt C, Carlson J, Dahm-Kahler P, Floter-Radestad A, et al. Lymphovascular space invasion as a predictive factor for lymph node metastases and survival in endometrioid endometrial cancer - a Swedish Gynecologic Cancer Group (SweGCG) study. Acta Oncol. 2019;58(11):1628-33.
14 Peters EEM, Leon-Castillo A, Hogdall E, Boennelycke M, Smit V, Hogdall C, et al. Substantial lymphovascular space invasion is an adverse prognostic factor in high-risk endometrial cancer. Int J Gynecol Pathol. 2022;41(3):227-34.
15 Bosse T, Peters EE, Creutzberg CL, Jurgenliemk-Schulz IM, Jobsen JJ, Mens JW, et al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer. 2015;51(13):1742-50.
16 Vermij L, Smit V, Nout R, Bosse T. Incorporation of molecular characteristics into endometrial cancer management. Histopathology. 2020;76(1):52-63.
17 Leon-Castillo A, Gilvazquez E, Nout R, Smit VT, McAlpine JN, McConechy M, et al. Clinicopathological and molecular characterisation of 'multiple-classifier' endometrial carcinomas. J Pathol. 2020;250(3):312-22.
18 Talhouk A, McConechy MK, Leung S, Li-Chang HH, Kwon JS, Melnyk N, et al. A clinically applicable molecular-based classification for endometrial cancers. Br J Cancer. 2015;113(2):299-310.
19 Stelloo E, Nout RA, Osse EM, Jürgenliemk-Schulz IJ, Jobsen JJ, Lutgens LC, et al. Improved risk assessment by integrating molecular and clinicopathological factors in early-stage endometrial cancer-combined analysis of the PORTEC cohorts. Clin Cancer Res. 2016;22(16):4215-24.
20 Talhouk A, McConechy MK, Leung S, Yang W, Lum A, Senz J, et al. Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer. Cancer. 2017;123(5):802-13.

21 Leon-Castillo A, de Boer SM, Powell ME, Mileshkin LR, Mackay HJ, Leary A, et al. Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: Impact on prognosis and benefit from adjuvant therapy. J Clin Oncol. 2020;38(29):3388-3397.

22 Antill Y, Kok PS, Robledo K, Yip S, Cummins M, Smith D, et al. Clinical activity of durvalumab for patients with advanced mismatch repair-deficient and repair-proficient endometrial cancer. A nonrandomized phase 2 clinical trial. J Immunother Cancer. 2021;9(6).

23 Oaknin A, Gilbert L, Tinker AV, Sabatier R, Boni V, O'Malley DM, et al. LBA36 - Safety and antitumor activity of dostarlimab in patients (pts) with advanced or recurrent DNA mismatch repair deficient (dMMR) or proficient (MMRp) endometrial cancer (EC): Results from GARNET. Ann Oncol. 2020;31:S1142-S215.

24 Konstantinopoulos PA, Luo W, Liu JF, Gulhan DC, Krasner C, Ishizuka JJ, et al. Phase II study of avelumab in patients with mismatch repair deficient and mismatch repair proficient recurrent/persistent endometrial cancer. J Clin Oncol. 2019;37(30):2786-94.

25 Lu KH, Dinh M, Kohlmann W, Watson P, Green J, Syngal S, et al. Gynecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome. Obstet Gynecol. 2005;105(3):569-74.

26 Win AK, Lindor NM, Winship I, Tucker KM, Buchanan DD, Young JP, et al. Risks of colorectal and other cancers after endometrial cancer for women with Lynch syndrome. J Natl Cancer Inst. 2013;105(4):274-9.

27 Casado A, González-Martín A, Rodolakis A, Taylor A, Westermann A, Zeimet AG, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Ann Oncol. 2015;27(1):16-41.

28 Astec study group, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. The Lancet. 2009;373(9658):125-36.

29 Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst. 2008;100(23):1707-16.

30 Rossi EC, Kowalski LD, Scalici J, Cantrell L, Schuler K, Hanna RK, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 2017;18(3):384-92.

31 Nout RA, Poll-Franse LVvd, Lybeert MLM, Wárlám-Rodenhuis CC, Jobsen JJ, Mens JWM, et al. Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the Post Operative Radiation Therapy in Endometrial Carcinoma 1 (PORTEC-1) trial. J Clin Oncol. 2011;29(13):1692-700.

32 Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004;92(3):744-51.

33 Blake P, Swart AM, Orton J, Kitchener H, Whelan T, Lukka H, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. The Lancet. 2009;373(9658):137-46.

34 Sorbe B, Nordstrom B, Maenpaa J, Kuhelj J, Kuhelj D, Okkan S, et al. Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: a controlled randomized study. Int J Gynecol Cancer. 2009;19(5):873.

35 Nout RA, Smit V, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens L, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. The Lancet. 2010;375(9717):816-23.

36 Wortman BG, Creutzberg CL, Putter H, Jürgenliemk-Schulz IM, Jobsen JJ, Lutgens LCHW, et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 20181;19(9):1067-1074

37 Sorbe B, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B. External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma--a prospective randomized study. Int J Radiat Oncol Biol Phys. 2012;82(3):1249-55.

38 Maggi R, Lissoni A, Spina F, Melpignano M, Zola P, Favalli G, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. Br J Cancer. 2006;95(3):266-71.

39 Susumu N, Sagae S, Udagawa Y, Niwa K, Kuramoto H, Satoh S, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. Gynecol Oncol. 2008;108(1):226.

40 Hogberg T, Signorelli M, de Oliveira CF, Fossati R, Lissoni AA, Sorbe B, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer. 2010;46(13):2422-31.

41 de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 2019;20(9):1273-1285.

42 Randall ME, Filiaci V, McMeekin DS, von Gruenigen V, Huang H, Yashar CM, et al. Phase III trial: Adjuvant pelvic radiation therapy versus vaginal brachytherapy plus paclitaxel/carboplatin in high-intermediate and high-risk early stage endometrial cancer. J Clin Oncol. 2019;37(21):1810-1818.

43 Matei D, Filiaci V, Randall ME, Mutch D, Steinhoff MM, DiSilvestro PA, et al. Adjuvant chemotherapy plus radiation for locally advanced endometrial cancer. N Engl J Med. 2019;380(24):2317-26.

44 van Weelden WJ, Massuger L, Enitec, Pijnenborg JMA, Romano A. Anti-estrogen treatment in endometrial cancer: A systematic review. Front Oncol. 2019;9:359.

45 Ethier JL, Desautels DN, Amir E, MacKay H. Is hormonal therapy effective in advanced endometrial cancer? A systematic review and meta-analysis. Gynecol Oncol. 2017;147(1):158-66.

46 Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 study. J Clin Oncol. 2020;38(1):1-10.

47 Oaknin A, Tinker AV, Gilbert L, Samouelian V, Mathews C, Brown J, et al. Clinical activity and safety of the anti-programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer: A nonrandomized phase 1 clinical trial. JAMA Oncol. 2020;6(11):1766-1772.

48 Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib plus pembrolizumab in patients With advanced endometrial cancer. J Clin Oncol. 2020;38(26):2981-2992.

49 Makker V, Colombo N, Casado Herraez A, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus pembrolizumab for advanced endometrial cancer. N Engl J Med. 2022;386(5):437-48.

50 de Boer SM, Nout RA, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LCHW, Van Der Steen-Banasik EM, et al. Long-term impact of endometrial cancer diagnosis and treatment on health-related quality of life and cancer survivorship: Results from the randomized PORTEC-2 trial. Int J Radiat Oncol Biol Phys. 2015;93(4):797-809.

51 de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-meder C, et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk randomised, phase 3 trial. Lancet Oncol. 2016;17(8):1-13.

52 Decruze SB, Green JA. Hormone therapy in advanced and recurrent endometrial cancer: a systematic review. Int J Gynecol Cancer. 2007;17(5):964-78.