Towards personalized treatment for high risk endometrial cancer

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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]

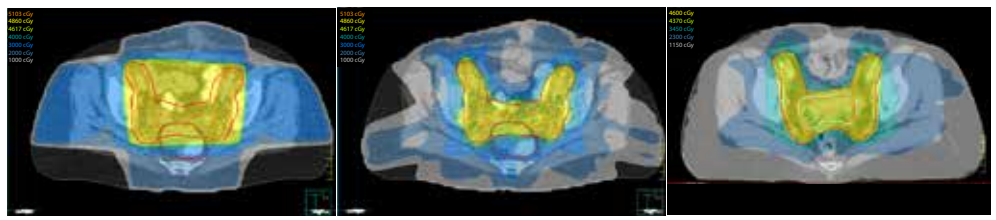

Figure 1. Examples of dose distributions of pelvic external beam radiotherapy for three different radiation techniques (A) 3-dimensional conformal radiotherapy, (B) intensity modulated radiotherapy and (C) volumetric modulated arc therapy.

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.

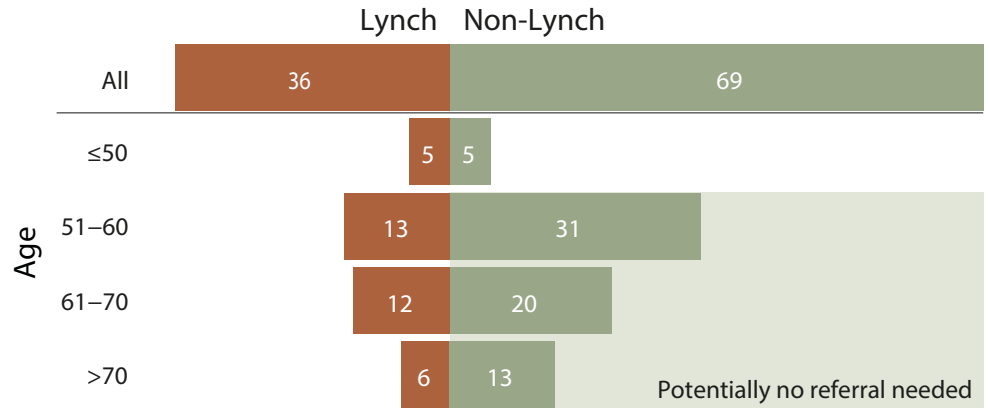

Figure 2. Distribution of Lynch syndrome suspected cases based on MMR-IHC and *MLH1*-hypermethylation assay. For patients aged 50 to 70 years with negative family history and those aged 70 years or older referral to a clinical geneticist could be omitted by identification of a somatic cause using sequencing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