Synopsis

Background Endometrial carcinoma is one of the most common cancer types in women, and incidence is increasing globally. Although many cancers are detected at an early stage and will be treated adequately with surgery alone, 15-20% of cancers will recur. After systemic recurrence, median survival approximates 7-12 months, in spite of treatment, with no improvement over the last decades. Our abilities to predict which patients will suffer recurrence, give ample room for improvement and robust prognostic biomarkers are needed to better recognise these high-risk patients. Response rates to medical treatment, both conventional and targeted, do not pass 40%, and are often considerably lower, even more so in the recurrent setting. Contrasting some other frequent cancer types such as breast and colorectal, in endometrial cancer algorithms, predictive biomarkers to support treatment choices are non-existent. Using preclinical models and large prospectively collected population-based patient series, potential biomarkers can be studied and tested at a pre-trial stage, which can accelerate the process of their identification and development, and increase the chance of successful trials.

Objectives We studied clinical and molecular variables for their abilities to function as prognostic or predictive biomarkers, with the ultimate aim to improve and individualise treatment strategies for endometrial cancer patients.
Exploring the behaviour of these biomarkers during cancer progression, followed as a logical consequence.

Materials and Methods For all studies included in this thesis (studies 1-5) clinical data, including follow-up data, has been analysed, and was retrieved either from the Haukeland University Hospital Series or from the significantly larger MoMaTEC series. The hyperplasia cohort has been studied in paper 4 and (paired) primary tumours and metastases in studies 4+5. From the biobank material, FFPE tissue has been used for immunohistochemistry (ARID1A; study 4, stathmin1; study 5), snap-frozen tissue for RNA microarrays (study 4) and haematoxylin stained frozen sections (study 3). For studies 1 and 2 only clinical data was used. Cell-line studies, including

dose response studies, viral transfection techniques and immunoblotting formed a strong basis under study 5.

Results After restaging all 1268 included patients, we demonstrated an improvement and simplification of the prognostic stratification using the FIGO 2009 version. In stage 1 patients, the myometrial infiltration depth was an independent prognostic factor, only for those patients that did not undergo lymphadenectomy. Cox multivariate survival analysis showed FIGO 2009 to be a stronger, independent prognostic factor than FIGO 1988. (study 1)

The 16% (207) tumours with discordant risk between preoperative and operative specimens, proved to be an interesting group with intermediate prognosis and risk of lymph node metastasis, in the entire dataset (n=1374) and in stage 1 tumours only (n=954). Cox multivariate survival analysis showed the risk classification to have independent prognostic value, and different hazard rates for the concordant high risk (HR 5.1) and discordant groups (HR 2.7 and 2.9). (study 2)

High tumour cell content (n=136, 50%) was in our series associated with more aggressive disease and reduced disease specific survival. (study 3)

Loss of ARID1A was linked to the endometrioid and clear cell subtypes, and associated with less aggressive disease, with the exception of the positive association with deep myometrial infiltration. No relation was found between loss of ARID1A and survival. Loss was noticed in a considerable percentage of the hyperplasias with atypia; this percentage further increased with disease progression. (study 4)

Stathmin1 knockdown in cell lines was associated with increased apoptosis after paclitaxel treatment. Patients with high stathmin1 level showed worse response to paclitaxel containing chemotherapy, but not to other treatments, compared to patients with normal stathmin level using RECIST criteria. In Cox multivariate analysis, stathmin1 was an independent predictor of survival only in the subgroup patients who received paclitaxel containing chemotherapy. (study 5)

Conclusions The FIGO 2009 classification system both simplified and improved prognostic stratification abilities compared to the previous system from 1988. (study 1)

Through integration of the preoperative histology with the final or operative histology, prognostic information can be further improved, especially when discordance between both results exists and results in the identification of subgroups with intermediate risk for metastatic spread and disease specific death that currently go unnoticed. (study 2)

The 80% tumour-cell content cutoff, meant to ensure high tumour purity, is, in endometrial cancer, associated with high-risk clinicopathological characteristics and reduced disease specific survival and may thus introduce an unintended selection bias. (study 3)

Loss of ARID1A occurs most in endometrioid and clear cell subtypes and is predominantly linked to clinicopathological parameters of less aggressive disease, but lacks correlation with survival. Loss starts early in endometrioid endometrial cancer carcinogenesis and further increases with tumour progression. (study 4)

Stathmin1 has potential as a predictive biomarker for response to paclitaxel containing chemotherapeutic regimes in endometrial cancer. (study 5)

Biomarker switch is a frequent phenomenon during endometrial cancrinoma disease progression and re-assessment of biomarker status in metastatic disease may be relevant. (study 4 and 5)