Abstract Thesis Jone Trovik

Endometrial carcinoma; can biomarkers aid in the prediction of aggressive disease?

A study with focus on preoperative tumour markers

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Background: Although endometrial cancer in general has a good prognosis, 15-20% recurs. Surgery is the main treatment with lymph node sampling increasingly advocated as compulsory for adequate staging. In metastatic disease, there is limited effect from systemic therapies including chemotherapy or antihormonal treatment No other targeted therapies are yet available in a routine clinical setting. To improve and individualise therapy for this patient group, improved tools for identification of high-risk patients, to tailor surgery in particular, and identification of targetable molecular alterations for development of more effective systemic therapies, are urgently needed. Several biomarkers including hormone receptor status, TP53 and Stathmin expression have been found to be of prognostic importance in retrospective studies. The PI3Kinase signalling pathway is over-expressed in aggressive endometrial carcinomas and PI3kinase inhibitors are entering clinical trials for treatment of metastatic disease.

Main objectives: The main objective was to evaluate if biomarkers, particularly examined in a preoperative setting, could identify aggressive endometrial carcinomas,

especially those with lymph node metastasis. An additional aim was to evaluate immunohistochemical markers potentially applicable as markers for response to antihormonal therapy and PI3Kinase-inhibitors. Also, we wanted to study changes in treatment strategy in relation to survival for endometrial carcinoma patients during a 30-year period in a population based setting.

Materials and methods: To evaluate potential biomarkers related to PI3Kinase signalling, a population based cohort was investigated for immunohistochemical expression of AKT, Phospho-AKT and Stathmin in hysterectomy specimens. These markers were also related to level of PI3Kinase signalling based on mRNA expression score in a prospective series of 76 patients (**Paper I**).

The prospective international multicenter study MoMaTEC; Molecular Markers in Treatment of Endometrial Cancer, recruited clinical data, tissue and blood samples from 1192 endometrial cancer patients treated at 10 different centres during 2001-2010. Preoperative curettage specimens and blood samples have been investigated for expression of a panel of potential biomarkers; Stathmin, Estrogen Receptor (ER), Progesterone Receptor (PR), TP53 and GDF-15 (**Paper II, III and IV**).

Changes in clinicopathological features and treatment were related to survival in a population based cohort of endometrial cancer patients from Hordaland County, Norway over the last 30 years (**Paper V**).

Results: Stathmin overexpression in hysterectomy specimens was strongly correlated with characteristics for aggressive disease and poor survival. PI3Kinase signalling activation was significantly associated with overexpression of Stathmin. Neither AKT nor phospho-AKT expression showed any significant correlations with clinicopathological factors nor PI3Kinase signalling levels (**Paper I**).

Overexpression of Stathmin validated to be correlated with aggressive disease in the large prospective multicentre setting (**Paper II**). Stathmin staining in curettage specimens was an independent predictor of lymph node metastases and overexpression

of Stathmin estimated in curettage and hysterectomy specimens were both independent predictors of poor survival.

High preoperative plasma GDF-15 level was significantly associated with aggressive disease. Adjusting for age and histological risk factors detected in preoperative biopsies, plasma GDF-15 independently predicted risk of lymph node metastasis. GDF-15 level also independently predicted poor prognosis (**Paper III**).

Pathologic expression of ER, PR and TP53 in preoperative curettage specimen correlated significantly with high age at diagnosis, high FIGO stage, non-endometrioid histology, high grade, metastatic nodes and poor prognosis in a large prospective multicenter setting. Double negative ER-PR independently predicted lymph node metastasis and poor survival. Even for the most favourable group of lymph node negative endometrioid tumours, ER-PR negative status influenced survival independent of tumour grade (**Paper IV**).

The number of endometrial cancer patients from Hordaland County increased significantly from 1981 through 2010 (**Paper V**), with a simultaneous increase in body mass index and decrease in disease stage at diagnosis. Routinely performed pelvic lymph node sampling increased, adjuvant radiotherapy was reduced and survival increased significantly during the same period.

Conclusions: Stathmin immunohistochemical staining is superior to AKT and phospho-AKT staining in detecting PI3Kinase signalling activation and endometrial carcinomas with poor outcome (**Paper I**).

Stathmin staining has been validated to identify endometrial carcinomas with aggressive clinic-pathological features in a large multicenter setting. Immunohistochemical staining for Stathmin in preoperative biopsies (curettage) independently predicts lymph node metastasis and poor survival (**Paper II**).

Plasma GDF-15 has been documented as elevated in two independent patient cohorts of endometrial cancer patients compared to controls. High preoperative GDF-15

plasma level was significantly correlated with aggressive subtypes and a significant and independent predictor for lymph node metastasis and poor survival (**Paper III**).

Double negative hormone receptor status (ER and PR negative) in preoperative endometrial cancer curettage has been validated to identify patients with poor prognosis in a prospective multicenter setting. ER-PR status independently predicts lymph node metastasis. (**Paper IV**).

During the 30-year period 1981 through 2010, a reduction in adjuvant radiotherapy and increase in routine pelvic lymphadenectomy and curative surgery with advanced disease, are associated with improved disease-specific- and overall survival in a population-based study of endometrial carcinoma patients with steadily increasing body mass index (**Paper V**).