

New Prognostic Markers In Stage III Serous Ovarian Adenocarcinomas

Akademisk Avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs
Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3
torsdagen den 5 juni 2008 kl. 9.00

av

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Avhandlingen baseras på följande arbeten:

- I **Partheen, K.**, Levan K., Osterberg, L., Helou, K., Horvath, G.
Analysis of cytogenetic alterations in stage III serous ovarian
adenocarcinoma reveals a heterogeneous group regarding survival, surgical
outcome, and substage.
Genes Chromosomes Cancer, 2004;40(4):342-8.
- II **Partheen, K.**, Levan K., Osterberg, L., Horvath, G.
Expression analysis of stage III serous ovarian adenocarcinoma distinguishes
a sub-group of survivors.
European Journal of Cancer, 2006;42(16):2846-54
- III **Partheen, K.**, Levan K., Osterberg, L., Claesson I., Fallenius G., Sundfeldt
K., Horvath G.
Four potential biomarkers as prognostic factors in stage III serous ovarian
adenocarcinomas.
Conditionally accepted in *International Journal of Cancer*
- IV **Partheen, K.**, Levan K., Osterberg, L., Claesson I., Sundfeldt K., Horvath G
External validation suggests Integrin Beta 3 (ITGB3) as prognostic
biomarker in serous ovarian adenocarcinomas.
Manuscript



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New Prognostic Markers In Stage III Serous Ovarian Adenocarcinomas

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ABSTRACT

Ovarian carcinoma is the fifth most common cause of cancer death in Swedish women. Patients with advanced-stage disease respond differently to treatment, and the clinical outcome is difficult to predict for an individual patient. To increase the knowledge about ovarian adenocarcinomas, we aimed to investigate genetic changes relevant to the growth and progression of advanced ovarian tumours. We classified the tumours on a biological basis to identify potential biomarkers for use as prognostic factors.

We analyzed the cytogenetic alterations with comparative genomic hybridization (CGH) and found significant differences in cytogenetic alterations in relation to survival, surgical outcome, and substage. Gain of regions at chromosome 1 and loss of regions at chromosome 4, 5, 8, 16, and X were common disparities associated with reduced survival.

Gene expression analysis with microarray revealed a subgroup of survivors with a specific genetic signature that may be associated with less aggressive tumour progression or with tumours more sensitive to treatment. Quantitative real-time polymerase chain reaction (QPCR) was used to evaluate potential biomarkers and to narrow down the number of relevant genes to study at the protein level. Four genes, *CLU*, *ITGB3*, *CAPG*, and *PRAME* were differently expressed in tumours from survivors and tumours from deceased patients. We used western blot for semiquantitative analysis of the corresponding proteins, and found a significant difference in expression concerning survival for all four proteins.

We performed an external validation of the four potential biomarkers in a new set of advanced ovarian adenocarcinomas. This established *ITGB3* (Integrin beta 3) as significantly differently expressed concerning survival. The loss of *ITGB3* expression in tumours from deceased patients and high expression in tumours from survivors could be used as a biomarker for patients with advanced serous tumours.

In conclusion, we have found cytogenetic changes and differences in gene and protein expressions between advanced ovarian adenocarcinomas from survivors and deceased patients. These differences indicate that it is possible to predict the clinical outcome with a biological model for ovarian cancer patients.

Key words: Ovarian cancer, biomarker, prognostic factors, Integrin beta 3

ISBN 978-91-628-7485-8

Göteborg 2008

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Link to thesis: <http://hdl.handle.net/2077/10126>