Molecular studies of lung cancer

Background:
Lung cancer is the most common cause of cancer related death. It is a heterogeneous disease at the molecular level. Further characterization of different molecular alterations in lung cancer may have future implications for development of therapies and biomarkers.

Aims/methods:
I: We mapped alterations in KIT and KITLG at the DNA, RNA and protein level in 72 primary lung cancer cases using array-based CGH, real-time qRT-PCR and immunohistochemistry, respectively.

II: To study the spectra and frequency of fusion genes in lung cancer from never-smokers, we will apply the RNA based NanoString technique on a large, retrospective, nation-wide and population-based tumor material (n=540).

III: We examine the prognostic power of RBM3 expression in two independent lung cancer cohorts (n=312 + 204) using immunohistochemistry.

IV: We aim to identify novel prognostic markers through a multicohort discovery and validation strategy using six publicly available gene expression datasets. Candidate markers will be further validated using immunohistochemistry.

Preliminary results:
I: Expression of KIT mRNA and protein correlated well, while expression was not affected by copy number alterations. Differences in KIT copy number, mRNA and protein expression were observed between histology groups.

II: In the first 46 cases analyzed, we found a high frequency of fusion genes among adenocarcinomas with wild-type/unknown EGFR-status (8/24 samples, 33%).

III: Cases with high nuclear RBM3 protein expression showed better prognosis, statistically significant in the largest cohort. In the same cohort, RBM3 expression remained an independent prognostic factor amongst adenocarcinoma cases in multivariable analysis (HR 0.54, 95% CI 0.33-0.9, p = 0.02).

IV: Our gene expression strategy identified 19 candidate markers. Out of these, three were chosen for immunohistochemical validation; Ki67, MCM4 and TYMS. A trend towards worse prognosis was seen in patients positive for Ki67 and MCM4 expression and results for TYMS were statistically significant.

Implications:
The studies bring a better understanding of alterations in lung cancer and may have future implications for development of clinically relevant testing strategies.

Published study: