Title of the Contribution:
Cathepsin B, plasminogen activator-inhibitor (PAI-1) and plasminogen activator-receptor (uPAR) are prognostic factors for patients with non-small cell lung cancer.

Abstract:
To evaluate the possible role of cysteine proteases and serine proteases, as well as their respective inhibitors and receptors, as new prognostic factors in NSCLC, we examined, for the first time, 10 biological parameters related to three proteolytic systems within a homogeneous collective of 147 cases of NSCLC. Activities (cath B(AT), cath B(A7.5)) and protein levels of cath B(C), cath L(C), uPA, PAI-1, uPAR [measured by three different assays uPAR (ADI), uPAR (HD13), uPAR (IIIF10)] and TF were measured in homogenates of lung tumour tissue and corresponding non-malignant lung parenchyma. Total cath B activity (cath B(AT)) and enzymatic activity of the fraction of cath B, which is stable and active at pH 7.5 (cath B(A7.5)), were determined by a fluorogenic assay using synthetic substrate Z-Arg-Arg-AMC. The concentrations of cath B(C), cath L(C), uPA, PAI-1, uPAR and TF were determined by ELISAs. uPAR was determined using three different ELISA formats. The median levels of cath B(AT) (5.1-fold), cath B(A7.5) (2.5-fold), cath B(C), (8.5-fold), cath L(C) (6.6-fold), uPA (6.5-fold), PAI-1 (4.2-fold), uPAR (ADI) (2.2-fold), uPAR (HD13) (4.0-fold) and uPAR (IIIF10) (2.6-fold) were higher in tumour tissue compared to the lung...
parenchyma. Cath B(AT), cath B(A7.5) and cath B(C) in primary tumours correlated with lymph node metastases. Regarding histologies, the concentration of PAI-1 seems to be associated with the histological cell types of NSCLC. We found the highest values of PAI-1 in large cell carcinoma> SCC, AC> carcinoid and lowest values in metastases of primary tumours of other organs. Only PAI-1 was significantly increased in poorly-differentiated cells (G3) compared to well- and moderately-differentiated cells (G1/G2). PAI-1 significantly correlated with cath B(AT) and cath B(A7.5) with uPAR (ADI), uPAR (HD13), uPAR (IIIIF10) with uPA, and only weakly with TF, but not with cath B(C) and cath L(C). Significant correlations with overall survival in the total population of NSCLC patients were observed in univariate analysis for cath B(AT), cath B(C), PAI-1, uPAR (ADI), uPAR (HD13), and uPAR (IIIIF10). Cath L(C) was not significantly associated with poor prognosis. Regarding the histological tumour type, only in patients with squamous cell carcinomas did cath B(A7.5) and PAI-1 remain significant prognostic factors. In multivariate survival analysis only two proteolytic factors, PAI-1 and uPAR (III101F), stayed significant. In conclusion, among 10 biological parameters evaluated within the same cohort of patients, only PAI-1, uPAR (ADI), uPAR (HD13), uPAR (IIIIF10), cath B(AT) and cath B(C) are prognostic factors for overall survival of NSCLC patients. Moreover, PAI-1 and uPAR (IIIIF10) add independent prognostic information with regard to established clinical and histomorphological factors in NSCLC.