P12 Prognosis of bladder cancer relapse based on urinary peptides detected by mass spectrometry

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Introduction & Objectives: Unraveling the molecular alterations during bladder cancer (BC) progression is crucial for guiding therapeutic interventions. Reliable biomarkers for patient stratification are needed for clinical use, but also for guiding clinical trials.
Previously reported urinary biomarkers highlighted the potential of proteomics for BC diagnosis and detection of relapse (Frantzi, Van Kessel et al. 2016)[1]. As a follow-up, in this study we aimed at deciphering molecular elements implicated in BC disease outcome to further introduce prognostic biomarkers.

Materials & Methods: Proteomics profiles of 98 patients previously acquired by capillary electrophoresis coupled to mass spectrometry (CE-MS) were evaluated. During the follow-up period of 5 years (median time of 15.7 months), 45 developed BC relapse and 53 were relapse-free.
Data analysis was performed by splitting the patient cohort into a training (n=48) and test set (n=50). Cox regression was performed for feature selection in the training set, considering only peptides detected in at least 30% of all samples (k = 1046). The analysis was repeated 10 times on 70% of randomly selected samples.
A random forest algorithm was consequently applied to integrate the significant biomarkers into a predictive model further validated in the test set. Positive predictive value, negative predictive value and concordance (Harrell C-statistic) were estimated based on the model performance in the test set.

Results:
36 peptides were identified as significant prognostic markers of BC relapse. Those were further integrated into a predictive model, showing significant prognostic value of BC relapse in the test set [HR = 5.76, p-value = 0.0001, c-index = 0.64].
The biomarkers included collagen fragments, fibrinogen A, nebulin, peptidoglycan recognition protein 1, forkhead box protein D2, CD99 antigen and ankyrin repeat domain-containing protein 36C.
A comparative analysis was performed considering TCGA gene expression data from 406 patients, confirming unfavorable prognosis for BC at increased Ankyrin repeat domain-containing protein 36C (HR=2.12), Forkhead box protein D2 (HR=3.11) collagen alpha-1 chains IV (HR=2.33), VI (HR=2.65), XIV (HR=3.15), alpha-3 chain IV (HR=8.75) and alpha-4 chain IV (HR=3.53) and favourable prognosis for Nebulin (HR=0.84). Additional comparisons considering early-stage BC transcriptomics profiles (study by Hedegaard J et al[2]) are currently ongoing.

Conclusions: Risk stratification strategies are essential for personalized management of BC. Prediction of BC relapse can assist in guiding intervention and build the foreground for prediction of treatment response. A follow-up investigation for correlating the prognostic markers with response to chemotherapy is ongoing.

References:

[1]Frantzi M, van Kessel KE, Zwarthoff EC et al. *Clin Cancer Res*. 2016 Aug 15;22(16):4077-86

[2]Hedegaard J, Lamy P, Nordentoft I et al. *Cancer Cell*. 2016 Jul 11;30(1):27-42