Metabolic Biomarkers for the Differential Diagnosis of Pancreatic Ductal Adenocarcinoma vs. Chronic Pancreatitis

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Background and Objective

The incidence of chronic pancreatitis (CP) varies between 4 and 23/100,000 in different populations, and has a tenfold higher prevalence. Chronic pancreatitis, in itself, is not only a risk factor (25-fold increased prevalence) for developing pancreatic cancer, but also greatly impairs the accuracy of diagnostic tests. In order to reduce health care costs and prolong patient survival, new diagnostic assays are needed. In a given population with an incidence of pancreatic cancer of 1.95%, a new assay has to perform with a minimum sensitivity of 88% at a specificity of 85% [1]. Our objective was to identify a panel of metabolites as biomarkers for this diagnostic purpose and such performance parameters.

Methods

For a retrospective case-control study in three tertiary referral centers, 914 patients were recruited having either pancreatic cancer (n=271), chronic pancreatitis (n=282) or liver cirrhosis (n=100). Subjects with non-pancreatic disease and blood donors served as controls (n=261). An initial exploratory study (n=202) was followed by multicenter studies for training (n=474, training set) and testing (n=239 testing set 1). Metabolite profiles of plasma and serum samples were generated from 477 metabolites (Figure 1+2) identified by high quality polar and lipid gas chromatography–mass spectrometry (GC–MS) and liquid chromatography–tandem mass spectrometry (LC–MS/MS).

Results

A panel consisting of 9 metabolites and CA19-9 is able to distinguish PDAC from chronic pancreatitis patients with an area under the curve (AUC) of 0.96, a fixed specificity of 85% and a sensitivity of 94.9% resulting in a negative predictive value (NPV) of 99.88% (ROC Curves, figure 3) in the training study when assuming an incidence of 1.95% of PDAC in the CP population.

The 9-metabolite plus CA19-9 panel detected 98% of resectable pancreatic cancer (55 out of 78, stageIA to IIIB, figure 4) with an accuracy of 90.4%.

An AUC of 0.94 in the testing set was determined.

A fixed cutoff of 0.384 was used for training and testing sets, resulting in a clinical performance of a specificity of 91.3%, and a sensitivity of 89.9%, resulting in a NPV of 99.78% (ROC Curve, figure 3).

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Conclusions

In a CP population with an increased risk for PDAC the performance of the biomarker panel would result in a negative predictive value of 99.9% [95% CI 99.7, 99.9] (training set) and 99.8% [95% CI 99.5, 99.9] (testing set) aiding physicians to optimize the timing for explorative surgery in patients at high risk for PDAC. In our study, this biomarker panel would have led to a significant reclassification of patients, with potentially major impacts on therapeutic choices and health care costs.