J Clin Exp Pathol 2015, 5:3
http://dx.doi.org/10.4172/2161-0681.S1.017

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4th International Conference and Exhibition on
Pathology

July 13-15, 2015 New Orleans, USA

Biomarkers for pancreatic cancer: Identification through meta-analysis and validation on tissue microarrays for potential clinical application

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Pancreatic cancer is common and aggressive: The main type is pancreatic ductal adenocarcinoma (PDAC). Establishing the diagnosis of PDAC is important for optimal patient management but can be difficult and relies on imaging and cytology/pathology. Although imaging may be highly suggestive of PDAC, a pathological diagnosis is preferred prior to definitive treatment; therefore tissue samples are required. Cytology samples are obtained at endoscopy. Cytological analysis requires the identification of different cell types and in particular the distinction of malignant pancreatic epithelial cells from reactive pancreatic cells and other gastrointestinal contaminants. This requires experience and expertise and can be difficult. A tissue diagnosis is not achieved in a significant proportion of PDAC cases. Hence, an unmet clinical need exists for the diagnosis of PDAC from cytological samples. One potential way of improving the cytological diagnosis is to use immunohistochemistry (IHC) biomarkers as an adjunct to cytology in difficult to diagnose cases. Diagnostic IHC biomarkers have been investigated, but to date none has entered into routine clinical practice. The aim of this study was to improve the diagnosis of PDAC from cytology samples. It is hoped that the identification and validation of IHC biomarkers in PDAC will help their clinical translation. For biomarker identification a meta-analysis of potential IHC diagnostic biomarkers investigated in PDAC was performed. Sixteen biomarkers were quantified and the highest ranked biomarkers according to pooled sensitivity/specificity values in resection specimens are: S100P (100% sensitivity/100% specificity); maspin (92%/97%); KOC (IMP3) (85%/98%); and MUC4 (82%/93%). Similarly, highest ranked biomarkers in cytology specimens are: KOC (85%/100%); SMAD4 (80%/100%); S100P (91%/91%); mesothelin (64%/92%); and MUC1 (83%/77%). These biomarkers have not entered into routine clinical practice partly because they were investigated in separate studies with relatively small sample sizes and without uniform and clinically appropriate cut-offs. Biomarkers identified in the meta-analysis were validated in a resection cohort from patients with pancreatico-biliary adenocarcinoma. The aim was to identify better biomarkers and cut-offs that could potentially be investigated in cytology samples. KOC, S100P, mesothelin and MUC1 were investigated in one set of tissue microarrays, while maspin was investigated in another set. Five cut-offs were carefully chosen for sensitivity/specificity analysis using receiver operating characteristics curve analysis. Using 20% positive cells as a cut-off achieved higher sensitivity/specificity values: KOC 84%/100%; S100P 83%/100%; mesothelin 88%/92%; MUC1 89%/63%; and maspin 96%/99%. Analysis of a panel of KOC, S100P and mesothelin achieved almost 100% sensitivity and specificity if at least two biomarkers were positive for both 10% and 20% cut-offs. A biomarker panel of KOC, S100P, maspin and mesothelin with at least 2 biomarkers positive was found to be an optimum panel in resection specimens from patients with PBA. Their diagnostic accuracies approach those of optimal conventional cytology. These markers may be appropriate for further clinical validation in cytology samples and potentially routine use in difficult cases.

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