KRAS and GNAS mutations in cell-free DNA and in circulating epithelial cells in patients with intraductal papillary mucinous neoplasms – an observational pilot-study regarding the risk of progression to pancreatic cancer

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Background & objectives

Intraductal papillary mucinous neoplasms (IPMN) belong to the pancreatic cystic benign neoplasms, of which some may progress into an invasive ductal pancreatic adenocarcinoma (PDAC). IPMNs are further divided into high-risk IPMN (main duct IPMNs and other IPMNs meeting high-risk stigmata) and low-risk IPMN (conservatively managed branch duct IPMN). For high-risk IPMNs, malignant progression into PDAC is about 40-92% in lifetime.
Our study evaluates the suitability of *KRAS* and *GNAS* mutated cell-free DNA (cfDNA) and circulating epithelial cells (CECs) as biomarkers for risk stratification in IPMN - by correlating their prevalence in blood samples with the current classification of high-risk and low-risk IPMNs.

Methods

We collected peripheral EDTA blood samples from patients who underwent surgery to remove high-risk IPMNs (n=19) or patients who are under clinical surveillance for branch duct (low-risk) IPMNs (n=18). All blood samples were processed for cfDNA isolation, before being screened for *KRAS* and *GNAS* mutations via digital-droplet PCR. A size-based cell separation system (Parsortix^{TM}) was used to identify CECs.

Results

Overall, *KRAS* mutations were found in 19% and *GNAS* mutations in 22% of cfDNA. Among the patients with high-risk IPMNs, which qualified for a surgical removal, the detection of *KRAS*

mutations was 21% and of *GNAS* mutations 37%. Among the patients with low-risk IPMNs, *KRAS* mutations were observed in 17% and *GNAS* mutations in 6%. Especially *GNAS* mutations in cfDNA were significantly more often observed in high-risk compared to low-risk IPMNs (p=0.042). Overall, 47% of high-risk and 17% of low-risk IPMNs showed either *KRAS* or *GNAS* mutations in cfDNA. In our cohort, no CECs could be detected.

Conclusion

In summary, especially the prevalence of *GNAS* mutations is higher in the group of high-risk IPMN patients who underwent surgery – compared to conservatively managed low-risk IPMNs -, which reflects the correlation of the mutations with potential for increased malignant progression. The results of this preliminary pilot-study justify future studies focusing on *GNAS* and on additional liquid biopsy markers.