Göteborg, 2018

ENDOSONOGRAPHY AND PRETREATMENT TUMOR PROFILING

- from sampling, staining, to sequencing

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, fredagen den 23 mars 2018, klockan 13:00

av

Per Hedenström

Fakultetsopponent:
Professor Lars Aabakken
University of Oslo, Norway

Avhandlingen baseras på följande delarbeten:

I. **EUS-guided reverse bevel fine-needle biopsy sampling and open tip fine-needle aspiration in solid pancreatic lesions - a prospective, comparative study.** Hedenström P, Demir A, Khodakaram K, Nilsson O, Sadik R. *Scand J Gastroenterol. 2018 Feb;53(2):231-237.*

II. **High clinical impact and diagnostic accuracy of EUS-guided biopsy sampling of subepithelial lesions: a prospective, comparative study.** Hedenström P, Marschall HU, Nilsson B, Demir A, Lindkvist B, Nilsson O, Sadik R. *Surg Endosc. 2018 Mar;32(3):1304-1313.*

III. **Characterizing gastrointestinal stromal tumors and evaluating neoadjuvant imatinib by sequencing of endoscopic ultrasound-biopsies.** Hedenström P, Nilsson B, Demir A, Andersson C, Enlund F, Nilsson O, Sadik R. *World J Gastroenterol. 2017 Aug 28;23(32):5925-5935.*

IV. **Pretreatment mutational analysis of *KIT* and *PDGFRA* optimizes down-sizing imatinib therapy of gastrointestinal stromal tumors.** Hedenström P, Andersson C, Sjövall H, Enlund F, Nilsson O, Nilsson B, Sadik R. *Manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN

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Abstract

Background and aims: Endosonography-guided fine needle aspiration (EUS-FNA) is imperfect in diagnosing solid pancreatic lesions (SPL) and subepithelial lesions (SEL) including gastrointestinal stromal tumors (GIST). In GISTs, imatinib therapy is effective only in variants of oncogenes *KIT* and *PDGFRA*. The global aim was to improve the EUS-diagnostics and study a biopsy approach (EUS-FNB) to obtain a reliable diagnosis of SPLs and SELs. In GISTs, the aim was to evaluate pretreatment samples for tumor risk assessment and the guidance of down-sizing imatinib therapy.

Methods: In two prospective, single-center studies (2012–2015), SPLs (n=68,*Paper I*) and SELs (n=70,*Paper II*) were sampled with EUS-FNA and EUS-FNB. A reference cohort (2006–2011) was used for comparison. The EUS-FNB-tissue of all GISTs (n=44) was subjected to Ki-67-indexing and DNA-sequencing of *KIT* and *PDGFRA* (*Paper III*). In a last study (*Paper IV*), pretreatment sequencing of GISTs (n=59) was performed.

Results: *Paper I*: In SPLs, EUS-FNB and EUS-FNA had a comparable diagnostic accuracy (69% *vs* 78%, p=0.31). The combination EUS-FNA+FNB was superior to EUS-FNA alone in pancreatic non-adenocarcinoma neoplasms (89% *vs* 69%, p=0.02). *Paper II*: In SELs, EUS-FNB had a higher diagnostic accuracy compared with EUS-FNA (83% *vs* 49%, p<0.001) leading to the reduced need for additional diagnostic procedures (14% *vs* 53%, p<0.001). *Paper III*: The EUS-FNB-tissue was diagnostic for GIST in 98%, accurate for Ki-67-indexing in 92%, and adequate for successful sequencing in 98% of the cases. In patients treated with down-sizing imatinib [*KIT* exon 11 (n=9); *PDGFRA* exon 12 (n=1)], the Ki-67-index was significantly higher in pretreatment FNB-tissue compared with resection specimens: $Ki\text{-}67_{DIFF}$ = 2.3 (95% CI: 0.67-5.37, p=0.005). *Paper IV*: Pretreatment sequencing, compared with no sequencing, lead to a higher rate of accurate down-sizing therapy (97% *vs* 70 %, p<0.001) and to the increased preoperative tumor size reduction on CT scan (32% *vs* 22%, p=0.036).

Conclusions: The performance of endosonography-guided fine-needle biopsy sampling has a significant diagnostic and clinical value in subepithelial lesions; especially in gastrointestinal stromal tumors. The acquired tissue is also accurate for the early tumor proliferation rate assessment and genetic profiling of GISTs. The suggested work-up approach facilitates the guidance and evaluation of down-sizing tyrosine kinase inhibitor therapy.

Keywords: endosonography, fine-needle biopsy, pancreatic neoplasms, gastrointestinal stromal tumors, *KIT*, *PDGFRA*, Ki-67, imatinib, neoadjuvant therapy

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