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 förvaras 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.

II. High clinical impact and diagnostic accuracy of EUS-guided biopsy sampling of subepithelial lesions: a prospective, comparative study.

III. Characterizing gastrointestinal stromal tumors and evaluating neoadjuvant imatinib by sequencing of endoscopic ultrasound-biopsies.

IV. Pretreatment mutational analysis of KIT and PDGFRA optimizes down-sizing imatinib therapy of gastrointestinal stromal tumors.
Manuscript
ENDOSONOGRAPHY AND PRETREATMENT TUMOR PROFILING
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Per Hedenström
Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden.

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-67DIFF = 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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