

Barrett's esophagus – aspects on early detection of malignant transformation

Akademisk avhandling
som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet, kommer att offentligas försvaras i Hjärtat, Sahlgrenska Universitetssjukhuset, Vita stråket 12, Göteborg, fredagen den 18 november 2016, klockan 13:00.

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Legitimerad läkare

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Avhandlingen baseras på följande delarbeten

- I. **Bratlie SO**, Johnsson E, Jönsson C, Fändriks L, Edebo A. Multiple-band imaging provides better value than white-light endoscopy in detection of dysplasia in patients with Barrett's esophagus. *Clinical Gastroenterology and Hepatology* 2015; 13: 1068-1074.
- II. **Bratlie SO**, Edebo A, Casselbrant A, Helander HF, Fändriks L. The renin-angiotensin system in Barrett's esophagus. *Scandinavian Journal of Gastroenterology* 2016; 9: 1037-1042.
- III. **Bratlie SO**, Casselbrant A, Edebo A, Fändriks L. The angiotensin II type 1 receptor as a potential biomarker for dysplasia in Barrett's esophagus. Submitted.
- IV. **Bratlie SO**, Wallenius V, Edebo A, Fändriks L, Casselbrant A. Proteomic approach to the potential role of angiotensin II in Barrett dysplasia. Manuscript.

**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER**



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ABSTRACT

Background: Barrett's esophagus (BE) is a metaplastic mucosal transformation adjacent to the gastroesophageal junction, due to chronic reflux of gastric juices. BE is associated to an increased risk of esophageal adenocarcinoma (EAC) development, preceded by different states of dysplasia. Early detection of dysplasia is of fundamental value for the patient because of the improved chances of curative treatment. International guidelines recommend endoscopic surveillance of BE. Because of the low incidence of EAC in the BE-population, better techniques for dysplasia detection during surveillance, and biomarkers for evaluation of cancer risk, are warranted for better selection of patients that will benefit from lifelong surveillance. The renin-angiotensin system (RAS) is involved in fluid and electrolyte homeostasis as well as in hemodynamic regulation. More recently, RAS has been associated to several pathology-related conditions such as inflammation and cancer. Epidemiological studies indicate that drugs interfering with RAS may alter the EAC-risk in a BE.

Objectives: The general aims of this thesis were to validate a new endoscopic technique for dysplasia detection, and to explore a number of RAS components as potential biomarkers for dysplasia in BE.

Methods: Patients were recruited from the endoscopy department at Sahlgrenska University Hospital. High-definition magnifying contrast enhanced endoscopy was compared to standard white light endoscopy for dysplasia yield. Biopsies were collected for histopathological evaluation. Immunohistochemistry was performed for the localization of RAS. RAS interfering drugs (ACE inhibitor or AT1R antagonist) were administered, in a randomized setting, for three weeks to patients with dysplasia in BE. Western blot was performed for targeted protein analyses, and proteomics was performed by 2-D gel electrophoresis and tandem mass spectrometry.

Results: In a randomized crossover setting, 107 patients were examined by advanced or standard endoscopy as the first investigation. An equal amount of patients were detected with dysplastic lesions in BE by the two techniques, but significantly fewer biopsies were acquired by the use of advanced endoscopy. The mucosal presence of the classical RAS components ACE, AT1R and AT2R were confirmed in both BE-patients and age matched non-BE controls. The AT1R expression was higher in the BE metaplastic mucosa of patients with dysplasia than in patients with no dysplasia. Several cancer-related proteins were found altered after three weeks of RAS-interfering medication (ACE inhibitor enalapril or AT1R antagonist candesartan) in dysplasia-bearing BE patients. A global proteomic analysis was performed in a subset of these patients, and three cancer-related proteins were identified as significantly regulated.

Conclusion: Advanced endoscopic technique provides a better dysplasia yield per biopsy compared to standard technology. The altered expression of RAS components and the impact of RAS interfering drugs on certain cancer-related proteins in BE dysplasia suggest involvement in carcinogenesis and support a biomarker potential.

Keywords: Barrett's esophagus, biomarker, cancer, endoscopy, esophageal adenocarcinoma, metaplasia, low-grade dysplasia, proteomics, renin-angiotensin system

ISBN 978-91-628-9935-6 (Print)

ISBN 978-91-628-9936-3 (PDF)

<http://hdl.handle.net/2077/44862>