Title: Improving Colorectal Cancer Screening: Using Narrow Band Imaging for Colonic Sessile Serrated Lesions Detection and Determining Their Risk Factors

Specific aims and hypotheses

Colorectal cancer (CRC) is a leading cause of morbidity and mortality in the world, especially in western countries [1, 2]. Worldwide, CRC accounts for nearly 700 000 deaths/year[2]. Colonoscopy has been shown to decrease both CRC incidence [3] and mortality by detecting and allowing the removal of adenomas [4-8], being endorsed as the preferred option for CRC screening and adenoma surveillance [9-14]. Adenomas are part of the carcinogenesis pathway of colorectal adenocarcinoma and they are particularly amenable to screening because of their slow growth and ease of endoscopic resection. However, optical colonoscopy has been shown to miss some of these lesions in tandem studies [15, 16], especially sessile serrated lesions (SSL). These lesions are different from adenomas, they are more frequent on the right colon, usually present with a flat morphology that makes them much harder to detect through optical colonoscopy. SSL also present a different, faster carcinogenesis pathway and as result of these characteristics, they are associated with interval CRC, which is the occurrence of colorectal cancer after screening colonoscopy and before the next scheduled screening procedure [17, 18].

New technologies are emerging to increase the sensitivity of colonoscopy for pre-cancerous lesions, especially adenomas, since their detection rate is associated with CRC future risk [19-22], but in order to increase the CRC preventive effect of colonoscopy it is also important to detect SSL more effectively. Narrow band imaging (NBI) has been to shown to be effective for SSL detection, but only in one trial performed in a single academic center and in a specific syndrome called sessile serrated polyposis [23, 24]. A recent RCT compared NBI (Olympus™ 190 series colonoscopes) and white light (WL) high definition colonoscopy for serrated lesions proximal to the sigmoid colon in average risk individuals and showed a trend towards higher detection in the NBI but failed to achieve statistical significance for the primary endpoint (number of proximal serrated lesions)[25]. Therefore, it's still unsettled whether NBI should be used systematically during colonoscopy to increase detection of CRC precursor lesions.

We hypothesize that the systematic usage of NBI during colonoscopy contributes to a higher rate of proximal SSL detection in a moderate CRC risk population.

The overall aim of the project is to improve endoscopic colorectal cancer screening, studying the effect of feasible interventions in the adenoma and the SSL detection rate.

The specific aims are:

1. **Compare the effectiveness in colon SSL detection of narrow band imaging versus high definition white light colonoscopy in a prospective randomized controlled trial (RCT).** Hypothesis: the systematic utilization of NBI during colonoscopy increases proximal SSL detection rate in the general population undergoing CRC screening colonoscopy and will increase colonoscopy effectiveness in decreasing interval CRC incidence.
2. **Study the risk factors for colonic SSL.** SSL risk factors are poorly characterized and include sex, age and smoking. Hypothesis: clinical and demographic characteristics may be predictive of SSL. We will perform an observational cross-sectional study using the cohort of patients submitted to colonoscopy in the RCT from aim 1.

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