学位論文の要約

# Endoscopy-focused primary, secondary and tertiary prevention of colorectal cancer

（内視鏡による大腸癌の一次、二次、三次予防）

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## 【BACKGROUND】

Colorectal cancer (CRC) is among the commonest and deadliest types of cancer. It is the second highest in economic burden among all cancers and the thirteenth of all diseases in Australia. In Japan, it has been gaining importance and in 2018 CRC was identified as second in incidence among all cancers for both women and men, and the leading cause of death amongst all cancers in women and the third leading cause of death in men. Research that can improve the prevention and treatment of this cancer is of the utmost importance.

## 【METHODS, RESULTS AND DISCUSSION】

In primary prevention, I studied the factors that contribute to the development of colorectal lesions (e.g. colorectal adenomas and sessile serrated adenomas/polyps). This was a prospective study carried out at the Lyell McEwin Hospital (South Australia) examining whether and by how much factors such as alcohol consumption and smoking are associated with colorectal lesions. A cohort of 291 procedures and 260 patients was recruited. In this cohort, we found that different factors are associated with different histologic subtypes of lesions. Furthermore, in terms of primary prevention of CRC, I sought to discover how to optimally conduct colonoscopy (e.g. in the morning or afternoon). This, added to research on the simplification of methods for assessing quality measures (e.g. adenoma detection rate – ADR – through adenoma detection quotient - ADQ), was aimed at optimising CRC screening programs. In the retrospective cohort of 2,657 procedures performed at the Lyell McEwin Hospital (South Australia), morning endoscopy lists were associated with better detection and ADQ was a reliable predictor of ADR.

With respect to secondary prevention, I undertook several studies. The main aim of these studies was to assess advanced endoscopic imaging (e.g. narrow band imaging - NBI) nationally and internationally, comparing different endoscopic classification methods for colorectal lesions to evaluate how well each performed. Two of our studies showed that the modified Sano's (MS) classification was the most accurate tool for predicting the histology of colorectal lesions during colonoscopy.

The first of these two studies involved a single centre randomised trial on 348 patients comparing the MS with the NBI international colorectal endoscopic (NICE) classification, but did not include the differentiation of sessile serrated adenomas/polyps (SSA/Ps) in the comparison. The second, a prospective study between Australia (exploratory phase with 483 colorectal lesions included) and Japan (validation phase with 30 colorectal lesions evaluated by four endoscopists), involved the comparison of the MS, NICE and Japan NBI expert team (JNET) classifications. The last two classifications were combined with the workgroup serrated polyps and polyposis (WASP) add-on to allow the comparison including SSA/Ps' differentiation.

The results from both studies were then used as a template for the development of a computer-aided diagnosis (CAD) system that could enable expert-level accuracy for any endoscopist. A CAD system was created, learning from 1,235 colorectal images, and tested with data from two different centres (Australia and Japan) and imaging technologies (i.e. NBI and blue laser imaging - BLI), showing results comparable to expert endoscopists. The mean AUC from the exploratory phase reached 94.3% (internal NBI dataset) while the mean AUCs for the validation phase scored 84.5% with the external NBI dataset and 90.3% with the external BLI dataset.

In addition to imaging, two other studies also focused on secondary prevention by specifically looking at (i) the different microbiota profile of early and invasive CRCs; and (ii) at the learning curve of colorectal endoscopic submucosal dissection (ESD). The former study, conducted at Nagoya University (Aichi prefecture) was based on DNA extraction of colonic mucosa brush and faecal samples from 25 patients and found to be statistically different relative to the abundance of several bacteria related with each type; this included the *Fusobacterium nucleatum* (a known bacterium species related to invasive CRC) as well as nine other genera of bacteria.

The latter study evaluated how the learning curve of the complex ESD procedure progressed in an expert Japanese endoscopy centre. This retrospective study comprised a large colorectal ESD database of 590 procedures (514 patients) performed by 26 endoscopists at Nagoya University Hospital (Aichi prefecture). Although the speed of dissection continuously improved throughout the years, ESD could be performed safely by non-experts.

Lastly, considering tertiary prevention, I evaluated the necessity of routine biopsies for the follow up of previous endoscopic resection of colorectal lesions, and proposed an innovative classification which provides a highly sensitive diagnosis of recurrence on a scar. This classification was conceived and prospectively explored at the Lyell McEwin Hospital (South Australia) with 100 scars (82 patients) and validated in five other countries in addition to Australia (i.e. Malaysia, Brazil, Japan, Singapore and United States of America) by 49 endoscopists where it achieved similar results.

## 【CONCLUSION】

The evidence produced during the research for this thesis has the potential to immediately influence not only research but also clinical practice related to primary, secondary and tertiary prevention of CRC. I strongly believe that this influence will contribute to improved clinical outcomes related to this burdensome disease.