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

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Abbreviations (alphabetical order)

ADR	adenoma detection rate
ASGE	American society for gastrointestinal endoscopy
BBPS	Boston bowel preparation scale
BLI	Blue laser imaging
BMI	body mass index
CAD	computer-aided diagnosis
CRC	colorectal cancer
EMR	endoscopic mucosal resection
ESD	endoscopic submucosal resection
Fn	*Fusobacterium nucleatum*
HGD	high grade dysplasia
HP	hyperplastic polyp
IEE	image enhancing endoscopy
JNET	Japan NBI expert team
LST	lateral spreading tumour
LST-G-H	LST granular homogeneous
LST-G-M	LST granular nodular mixed
LST-NG	LST non-granular
MS	modified Sano's
NBI	narrow band imaging
NBI-DF	NBI with dual focus magnification
NICE	NBI international colorectal endoscopic
PIVI	preservation and incorporation of valuable endoscopic innovations
SSA/P	sessile serrated adenoma/polyp
TA	tubular adenoma
TVA	tubulovillous adenoma
VA	villous adenoma
WASP	workgroup serrated polyps and polyposis

Declaration

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List of figures in the thesis
separate from submissions and publications

Scholarly activity

Peer-reviewed journal papers (published, in press or submitted) included in this thesis, in order of appearance

Singh R, **Zorrón Cheng Tao Pu L**, Koay D, Burt A. Sessile serrated adenoma/polyps: where are we at in 2016? World J Gastroenterol. 2016 Sep 14;22(34):7754-9. doi: 10.3748/wjg.v22.i34.7754. (Chapter 2)

Zorron Cheng Tao Pu L, Khizar R, Singh G, Nakamura M, Yamamura T, Koay DSC, Ovenden A, Edwards S, Ruszkiewicz A, Hirooka Y, Fujishiro M, Burt AD, Singh R. Different factors are associated with conventional adenoma and serrated colorectal neoplasia. Nagoya J Med Sci. 82; 335-343; doi 10.18999/nagjms.82.2.335 2020. (Chapter 3)

Zorron Cheng Tao Pu L, Lu K, Ovenden A, Rana K, Singh G, Krishnamurthi S, Edwards S, Wilson B, Nakamura M, Yamamura T, Ruszkiewicz A, Hirooka Y, Burt AD, Singh R. Effect of time of day and specialty on polyp detection rates in Australia. J Gastroenterol Hepatol. 2019 May;34(5):899-906. doi: 10.1111/jgh.14566. Epub 2019 Jan 8. (Chapter 4)

Zorron Cheng Tao Pu L, Singh G, Rana K, Nakamura M, Yamamura T, Krishnamurthi S, Ovenden A, Edwards S, Ruszkiewicz A, Hirooka Y, Fujishiro M, Burt AD, Singh R. Polyp detection rate as a surrogate for adenoma and sessile serrated adenoma/polyp detection rates. Gastrointest Tumors. 2020. doi 10.1159/000505622. (Chapter 5)

Pu LZCT, Cheong KL, Koay DSC, Yeap SP, Ovenden A, Raju M, Ruszkiewicz A, Chiu PW, Lau JY, Singh R. Randomised controlled trial comparing modified Sano's and narrow band imaging international colorectal endoscopic classifications for colorectal lesions. World J Gastrointest Endosc. 2018 Sep 16;10(9):210-218. doi: 10.4253/wjge.v10.i9.210. (Chapter 6)

Zorron Cheng Tao Pu L, Yamamura T, Nakamura M, Koay DSC, Ovenden A, Edwards S, Burt AD, Hirooka Y, Fujishiro M, Singh R. Comparison of different virtual chromoendoscopy classification systems for the characterization of colorectal lesions. JGH Open. *Accepted* 2020. (Chapter 7)

Zorron Cheng Tao Pu L, Maicas G, Tian Y, Yamamura T, Nakamura M, Suzuki H, Singh G, Rana K, Hirooka Y, Fujishiro M, Burt AD, Carneiro G, Singh R. Computer-aided diagnosis for characterization of colorectal lesions: comprehensive software including serrated lesions. Gastrointest Endosc. 2020 Mar 4;S0016-5107(20)30218-2. doi: 10.1016/j.gie.2020.02.042. Online ahead of print. (Chapter 8)

Zorron Cheng Tao Pu L, Yamamoto K, Honda T, Nakamura M, Yamamura T, Hattori S, Burt AD, Singh R, Hirooka Y, Fujishiro M. Microbiota profile is different for early and invasive colorectal cancer and is consistent throughout the colon. J Gastroenterol Hepatol. 2020 Mar;35(3):433-437. doi: 10.1111/jgh.14868. Epub 2019 Oct 23. (Chapter 9)

Zorron Cheng Tao Pu L, Nakamura M, Yamamura T, Esaki M, Kaosombatwattana U, Rodriguez MR, Edwards S, Burt AD, Singh R, Hirooka Y, Fujishiro M. Learning curve for mastery of colorectal endoscopic submucosal dissection: perspectives from a large Japanese cohort. JGH open. doi:10.1002/jgh3.12298 2020. (Chapter 10)

Zorron Cheng Tao Pu L, Chiam KH, Yamamura T, Nakamura M, Berzin TM, Mir FF, Hourneaux de Moura EG, Madruga Neto AC, Ching Koay DS, Loong CK, Ovenden A, Edwards S, Burt AD, Hirooka Y, Fujishiro M, Singh R. Narrow band imaging for scar (NBI-SCAR) classification: from conception to multicenter validation. Gastrointest Endosc. 2020 May;91(5):1146-1154.e5. doi: 10.1016/j.gie.2019.08.036. Epub 2019 Sep 5. (Chapter 11)

Other publications

Peer reviewed journals

Froessler B, **Zorron Cheng Tao Pu L**, Aboustate N, Ovenden A, Singh R. Dynamic functional clot formation in patients undergoing endoscopic mucosal resection. JGH Open. 2020. doi:10.1002/jgh3.12306.

Carneiro G, **Zorron Cheng Tao Pu L**, Singh R, Burt AD. Deep learning uncertainty and confidence calibration for the five-class polyp classification from colonoscopy. Med Image Anal. 2020 May;62:101653. doi: 10.1016/j.media.2020.101653. Epub 2020 Feb 28.

Chiam KH, Leiria F, **Zorron Cheng Tao Pu L**, Choi KC, Singh R. Chromoendoscopy: role in modern endoscopic imaging. Transl Gastroenterol Hepatol. Received: 24 September 2019; Accepted: 04 December 2019; Published: 05 July 2020. doi: 10.21037/tgh.2019.12.06.

Koay DSC, Ghumman A, **Pu LZCT**, Singh R. Narrow-band imaging with magnification and the water immersion technique: a case-finding, cost-effective approach to diagnose villous atrophy. Singapore Med J. 2019 Oct;60(10):522-525. doi: 10.11622/smedj.2019131.

Kwan M, Cheong KL, Koay DSC, **Zorron Cheng Tao Pu L**, Singh R. A prospective randomised controlled trial comparing carbon dioxide and air insufflation during ERCP: is it worth the pain? GastroHep. 2019; 1: 5-10. https://doi.org/10.1002/ygh2.185.

Krishnamurthi S, Rana K, Singh G, **Zorron Cheng Tao Pu L**, Singh R. False sense of security: a case of retroperitoneal perforation after colonic EMR. VideoGIE. 2018 Feb 22;3(4):121-122. doi: 10.1016/j.vgie.2018.01.006. eCollection 2018 Apr.

Singh R, Cheong KL, **Zorron Cheng Tao Pu L**, Mangira D, Koay DSC, Kee C, Ng SC, Rerknimitr R, Aniwan S, Ang TL, Goh KL, Ho SH, Lau JY. Multicenter randomised controlled trial comparing the high definition white light endoscopy and the bright narrow band imaging for colon polyps. World J Gastrointest Endosc. 2017 Jun 16;9(6):273-281. doi: 10.4253/wjge.v9.i6.273.

Zorron Cheng Tao Pu L, Singh R. Topical antispasmodics during colonoscopy: do they have a role? Endosc Int Open. 2017 Jun;5(6):E408-E409. doi: 10.1055/s-0043-106580. Epub 2017 May 31.

Book chapters

Zorron Cheng Tao Pu L, Chiu P, Singh R. Endoscopic submucosal dissection for the esophagus. In: Endoscopy in Early Gastrointestinal Cancers, Volume 2: Treatment – Chapter 4. Edited by: Prof Tajiri H et cols. Ed: Springer. Published 2020. eBook ISBN 978-981-10-6778-5. doi: 10.1007/978-981-10-6778-5. Hardcover ISBN 978-981-10-6777-8.

Zorron Cheng Tao Pu L, Benerjee R, Singh R. Diagnosis of superficial esophageal neoplasia: classification. In: Endoscopy in Early Gastrointestinal Cancers, Volume 1: Diagnosis – Chapter 4. Edited by: Prof Sung J et cols. Ed: Springer. Published 2020. eBook ISBN 978-981-10-6769-3. doi: 10.1007/978-981-10-6769-3. Hardcover ISBN 978-981-10-6768-6.

Koay DSC, **Zorron Cheng Tao Pu L**, Singh R. Endoscopic diagnosis of Barrett's esophagus and early adenocarcinoma. In: Endoscopy in Early Gastrointestinal Cancers, Volume 1: Diagnosis – Chapter 7. Edited by: Prof Sung J et cols. Ed: Springer. Published 2020. eBook ISBN 978-981-10-6769-3. doi: 10.1007/978-981-10-6769-3. Hardcover ISBN 978-981-10-6768-6.

Zorron Cheng Tao Pu L, Rocha RSP, Artifon ELA, de Moura EGH, Sakai P. Metallic stents for the biliary tree. In: Série Manual do Médico-Residente - Endoscopia Baseada em Evidências – Chapter 9.6. Edited by: Prof Eduardo GH de Moura et cols. Ed: Atheneu 2017 – ISBN: 9788538808268

Published conference presentations

Presentations that received a prize or award are identified with an asterisk.

Australian Gastroenterology Week 2019 (AGW 2019) – **September/2019 – Adelaide – Australia**

Zorron Cheng Tao Pu L, et al. Narrow band imaging for scar (NBI-SCAR) classification: from conception to multicentre validation. Oral presentation. J Gastroenterol Hepatol. 2019; 34 (Suppl 2): 227-8. doi:10.1111/jgh.14796.

Zorron Cheng Tao Pu L, et al. Prospective study assessing a comprehensive computer-aided diagnosis for characterisation of colorectal lesions: results from different centres and imaging technologies. Oral presentation. J Gastroenterol Hepatol. 2019; 34 (Suppl 2): 25-6. doi:10.1111/jgh.14796.

* Zorron Cheng Tao Pu L, et al. Modified Sano's (MS) is the most accurate classification for characterising serrated polyps and adenomas with different virtual chromoendoscopy methods: results of a prospective observational study. Poster presentation. J Gastroenterol Hepatol. 2019; 34 (Suppl 2): 226-7. doi:10.1111/jgh.14796.

Zorron Cheng Tao Pu L, et al. Microbiota profile is markedly different for early and invasive colorectal cancer; and is consistent throughout the colon. Poster presentation. J Gastroenterol Hepatol. 2019; 34 (Suppl 2): 40-1. doi:10.1111/jgh.14796.

Zorron Cheng Tao Pu L, et al. Learning curve for mastery of colorectal endoscopic submucosal dissection: perspectives from a Japanese cohort of over 500 procedures. Poster presentation. J Gastroenterol Hepatol. 2019; 34 (Suppl 2): 20-1. doi:10.1111/jgh.14796.

Pu L, et al. Endoscopic mucosal resection of duodenal polyps: outcomes from a single center. Poster presentation. J Gastroenterol Hepatol. 2019; 34 (Suppl 2): 14. doi:10.1111/jgh.14796.

Pu L, et al. Endoscopic submucosal dissection of the gastrointestinal tract: experience outside East Asia. Poster presentation. J Gastroenterol Hepatol. 2019; 34 (Suppl 2): 16. doi:10.1111/jgh.14796.

Hajelssedig OE, Cheng Tao Pu L, et al. Narrow band imaging endoscopy with targeted biopsies versus standard endoscopy with random biopsies in patients with Barrett's oesophagus: a meta-analysis. Poster presentation. J Gastroenterol Hepatol. 2019; 34 (Suppl 2): 214-15. doi:10.1111/jgh.14796.

Australian Gastroenterology Week 2018 (AGW 2018) – **September/2018 – Brisbane – Australia 14 184-186**

Zorron Cheng Tao Pu L, et al. Prospective study predicting histology in colorectal lesions using wNICE, wJNET and MS classifications. Oral presentation. J Gastroenterol Hepatol. 2018; 33 (Suppl 2): 14. doi: 10.1111/jgh.14390.

Zorron Cheng Tao Pu L, et al. Effect of training and time of the day on polyp detection rates. Oral presentation. J Gastroenterol Hepatol. 2018; 33 (Suppl 2): 184-5. doi: 10.1111/jgh.14390.

Zorron Cheng Tao Pu L, et al. Prevalence and distribution of serrated polyps in the colon. Poster presentation. J Gastroenterol Hepatol. 2018; 33 (Suppl 2): 185-6. doi: 10.1111/jgh.14390.

Zorron Cheng Tao Pu L, et al. Prospective study assessing associated factors in patients with colorectal lesions. Poster presentation. J Gastroenterol Hepatol. 2018; 33 (Suppl 2): 186. doi: 10.1111/jgh.14390.

Digestive Diseases Week 2018 (DDW 2018) –

June/2018 – Washington/DC – United States of America

Zorron Cheng Tao Pu L, et al. Computer-aided diagnosis for characterising colorectal lesions: interim results of a newly developed software. Poster presentation. Gastrointest Endosc. 2018; 87 (6, Suppl): AB245. doi: 10.1016/j.gie.2018.04.1406.

Zorron Cheng Tao Pu L, et al. Effect of training and time of the day on polyp detection rates in Australia. Poster presentation. Gastrointest Endosc. 2018; 87 (6, Suppl): AB161. doi: 10.1016/j.gie.2018.04.1406.

Zorron Cheng Tao Pu L, et al. Optical evaluation of scars after EMR using NBI with dual focus and underwater technique (uNBI-DF): interim analysis. Poster presentation. Gastrointest Endosc. 2018; 87 (6, Suppl): AB377. doi: 10.1016/j.gie.2018.04.1406.

Asian Pacific Digestive Week 2017 (APDW 2017) –

September/2017 – Hong Kong – Hong Kong

Cheng LZTP, et al. Computer-aided diagnosis (CAD) for characterising colorectal lesions: initial results of a newly developed software. Oral presentation – e-poster. J Gastroenterol Hepatol. 2017; 32 (Suppl 3): 251. doi: 10.1111/jgh.13881.

Cheng LZTP, et al. Prospective study predicting histology in colorectal lesions: interim analysis of the NICE, JNET and MS classifications. Oral presentation – e-poster. J Gastroenterol Hepatol. 2017; 32 (Suppl 3): 252. doi: 10.1111/jgh.13881.

Cheng LZTP, et al. Prospective study to evaluate scars after colorectal EMR using NBI with dual focus and underwater technique (uNBI-DF): interim analysis. Oral presentation – e-poster. J Gastroenterol Hepatol. 2017; 32 (Suppl 3): 252. doi: 10.1111/jgh.13881.

Cheng LZTP, et al. Prospective study assessing associated factors for colorectal lesions: interim analysis. Oral presentation – e-poster. J Gastroenterol Hepatol. 2017; 32 (Suppl 3): 253-4. doi: 10.1111/jgh.13881.

Koay DSC, Cheng LZPT, et al. Duodenal Brunner's gland cyst presenting with a false 'target sign': a case report. Poster presentation. J Gastroenterol Hepatol. 2017; 32 (Suppl 3): 259-60. doi: 10.1111/jgh.13881.

Cheng LZPT, et al. A caecal gangliocytic paraganglioma: a cause for concern? Poster presentation. J Gastroenterol Hepatol. 2017; 32 (Suppl 3): 260. doi: 10.1111/jgh.13881.

Australian Gastroenterology Week 2017 (AGW 2017) –

August/2017 – Gold Coast/QLD – Australia

Pu LZCT, et al. Prospective study predicting histology in colorectal lesions: interim analysis of the NICE, JNET and MS classifications. Oral presentation. J Gastroenterol Hepatol. 2017; 32 (Suppl 3): 34. doi: 10.1111/jgh.13889.

Pu LZCT, et al. Prospective study assessing associated factors for colorectal lesions: interim analysis. Oral presentation. J Gastroenterol Hepatol. 2017; 32 (Suppl 3): 33. doi: 10.1111/jgh.13889.

Pu LZCT, et al. Computer-aided diagnosis (CAD) for characterizing colorectal lesions: initial results of a newly developed software. Poster presentation. J Gastroenterol Hepatol. 2017; 32 (Suppl 2): 34-5. doi: 10.1111/jgh.13889.

Pu LZCT, et al. Prospective study to evaluate scars after colorectal endoscopic mucosal resection using narrow-band imaging with dual focus and underwater technique: interim analysis. Poster presentation. J Gastroenterol Hepatol. 2017; 32 (Suppl 3): 33-4. doi: 10.1111/jgh.13889.

Koay DSC, Pu LZCT, et al. Duodenal Brunner's gland cyst presenting with a false 'target sign': a case report. Poster presentation. J Gastroenterol Hepatol. 2017; 32 (Suppl 3): 43-4. doi: 10.1111/jgh.13889.

Pu LZCT, et al. A caecal Gangliocytic paraganglioma: a cause for concern? Poster presentation. J Gastroenterol Hepatol. 2017; 32 (Suppl 3): 32-3. doi: 10.1111/jgh.13889.

Prizes and awards

- **Research & Business Partnerships Prize** (13th Florey Conference) - September/2019 - Adelaide/Australia
- **Poster of Merit** (AGW 2019) - September/2019 - Adelaide/Australia
- **Best Presenter Award** (JDDW 2018) - November/2018 - Kobe/Japan
- **Outstanding Poster Award** (JDDW 2018) - November/2018 - Kobe/Japan
- **John Barker Prize** (11th Florey Conference) - September/2017 – Adelaide/Australia
- **Florey Medical Research Foundation Prize** (11th Florey Conference) - September/2017 – Adelaide/Australia

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Abstract

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.

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) 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.

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.

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

Chapter 1

Introduction to the research

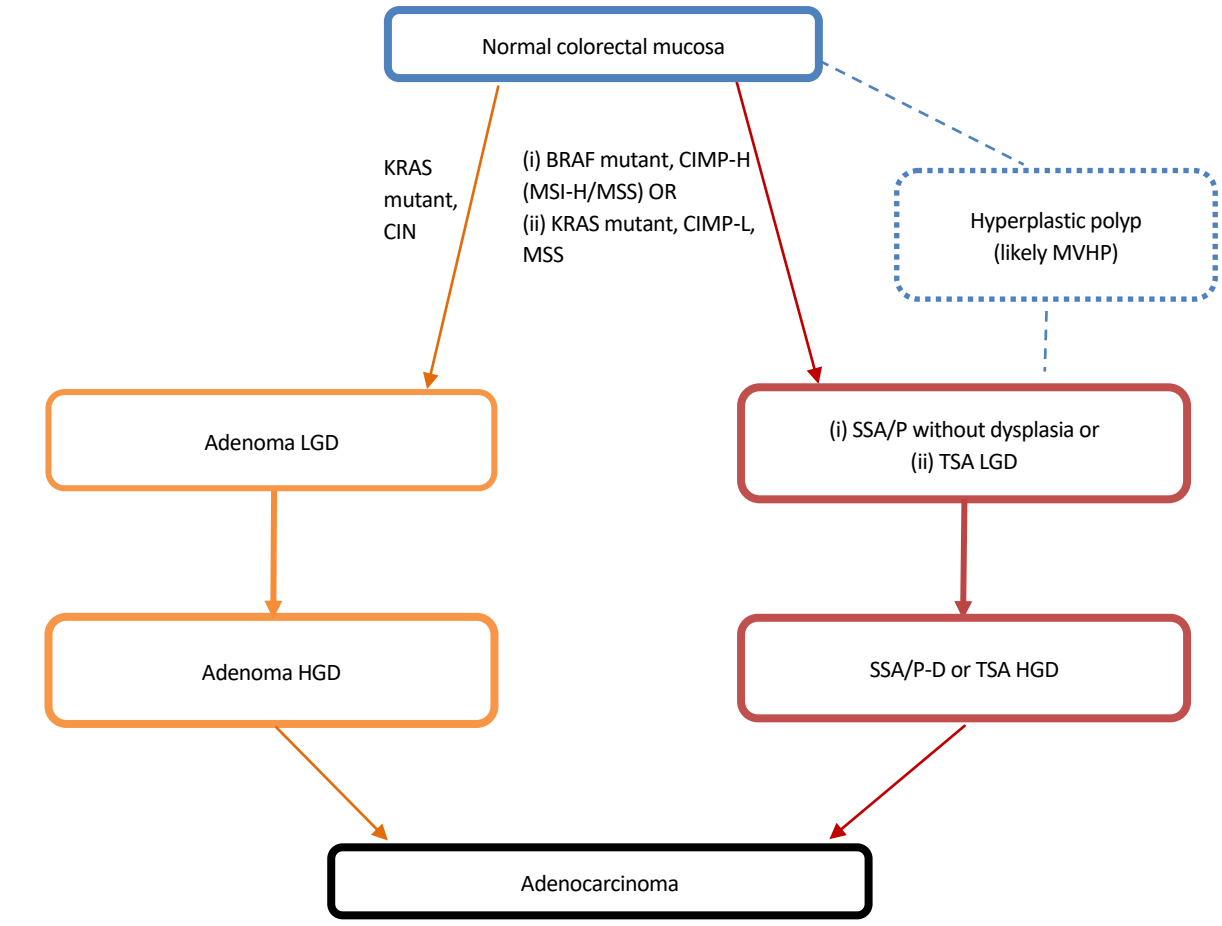
1.1 Primary prevention of colorectal cancer

In Australia, colorectal cancer (CRC) is the second commonest cause of death by cancer in Australia (behind lung cancer) and the third most commonly diagnosed cancer (behind breast and prostate). Australia is estimated to have had in 2019 approximately 16.400 new cases (54.1:100,000) and 5,600 deaths (17.8:100,000), as reported by the Australian Institute of Health and Welfare[1]. In Japan, CRC is identified as second in incidence (15%) among all cancers for both women (behind breast) and men (behind stomach), with an estimation of 152,100 new cases in 2018 (120.3:100,000). CRC was the leading cause of death amongst all cancers in women (16%) and the third leading cause of death in men (13%), responsible for over 53,000 deaths (42.3:100,000) in 2018[2].

1.1.1 Colorectal cancer and polyps

Colorectal cancer most commonly arises from colorectal polyps, although not every polyp has precancerous features. Several histological subtypes, such as inflammatory, diminutive hyperplastic and hamartomatous, are not associated with CRC[3]. On the other hand, adenomas or conventional adenomas, sessile serrated adenomas/polyps (SSA/Ps) and traditional serrated adenomas (TSAs) are thought to be responsible for almost all of colorectal adenocarcinomas[4], which represent the vast majority of CRCs[5]. As there is overlap in the nomenclature of early CRC and advanced polyps, CRCs and colorectal polyps can be addressed as one within the broader term colorectal lesion.

Colorectal lesions are associated with specific genetic mutations which are believed to contribute to their malignancy potential. KRAS gene mutation and chromosome instability (CIN) have been correlated with adenomas and older age in CRC patients[6,7]. This is also known as the adenoma-adenocarcinoma pathway. On the other hand, BRAF gene mutation (and sometimes KRAS mutation) has been associated with cancer in younger individuals, and with the serrated histology. These features led to the description of the serrated pathway. Interestingly, the contribution of serrated polyps to CRC seems to be excessively high in relation to their prevalence. One hypothesis is that neoplastic serrated polyps evolve more rapidly to invasive cancer once they become dysplastic[8,9]. Another hypothesis is that due to its inconspicuous features, SSA/Ps are being missed[10,11]. Moreover, the microvesicular subtype of hyperplastic polyp has been associated with the CpG island methylator phenotype (CIMP), which can ultimately lead to microsatellite instability (MSI) and transformation into SSA/Ps[12]. The main pathways leading to CRC have been illustrated in Figure 1.



KRAS	KRAS proto-oncogene, GTPase	LGD	Low grade dysplasia
CIN	Cromossonal instability	HGD	High grade dysplasia
BRAF	B-raf proto-oncogene, serine/threonine kinase	TSA	Traditional serrated adenoma
CIMP-L	CpG island methylator phenotype low	SSA/P	Sessile serrated adenoma/polyp
CIMP-H	CpG island methylator phenotype high	- - -	Hypothesised pathway from HP to SSA/P
MSS	Microssatelite stable	→	Serrated pathway
MSI-L	Microssatelite instability low	→	Conventional adenoma pathway
MSI-H	Microssatelite instability high		
MVHP	Microvesicular hyperplastic polyp		

Figure 1.1 Simplified molecular model for development of CRC through the conventional adenoma and serrated pathways (adapted from Bettington *et al.*[4] and Pino *et al.*[6])

Despite many studies, there is still controversy in the field of pathology around the histological diagnosis of SSA/Ps. A clear standard to be employed unequivocally and globally is still lacking. The World Health Organization (WHO) contributed greatly to a solution for this problem in 2010[13], when the organisation specified several criteria that should be observed in order to diagnose SSA/Ps. These criteria were further improved by the Japanese Society for Cancer of the Colon and Rectum (JSCCR), with some further contribution by Shida et al.[14] Due to variants in diagnostic criteria, however, epidemiological studies on serrated polyps and specific subtypes (HPs, SSA/Ps and TSAs) are scarce and have produced variable results.

Screening programs. As noted, the overall pathways from normal mucosa to CRC are mostly known. Although displaying molecular and histological differences, the common pathways almost always encompass a precancerous lesion (i.e. colorectal polyp). The precancerous step takes a variable amount of time before transforming into CRC, depending on the polyp histological type. Nevertheless, however variable it is, this period of time provides a window of opportunity for preventing cancer and hence makes CRC eligible for a screening program. According to the WHO, the definition of screening is the

> *Presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population.*[15]

The protocols for utilising a screening program endorsed by the WHO were initially described in 1968 by Wilson and Jungner[16], but summarised by the German Institute for Quality and Efficiency in Health Care in 2013 (updated in 2016)[17]. The WHO highlight the necessity of weighing risks and costs associated with the screening test on the one side, and the benefits and cost savings of early detection and treatment of the disease on the other. The recommendation is to pursue a screening program for diseases that fulfil the following criteria:

- Screening should be done only for diseases with serious consequences, so that screening tests could potentially have clear benefits to people's health.
- The test must be reliable enough, and not harmful in itself.
- There must be an effective treatment for the disease when detected at an early stage – and there has to be scientific proof that that treatment is more effective when started before symptoms arise.
- Neutral information should be made available to the public, to help people decide for themselves whether or not to have a screening test.

Therefore, as already identified half a century ago, CRC makes a great model for a screening program. The most cost-effective population screening protocol continues to be debated, and slightly different strategies have been used around the globe[18,19]. Although for population screening programs it is common for the first step to be a non-invasive faecal occult blood test (followed by colonoscopy when positive), for opportunistic screening, a colonoscopy is commonly found to be the first step. Most countries recommend screening for CRC between 50 and 75 years of age, although other factors, such as family history of CRC, are usually taken into consideration.

In all cases, using colonoscopy as a screening tool for CRC (either as first or second step) is an effective way of preventing CRC by removing colorectal lesions. This means CRC is a preventable cancer once its precursor is removed, and screening for colorectal lesions has been proven to be cost-effective for this purpose[20].

The impact of screening programs is not only in the prevention of CRC but also in allowing an early diagnosis. An early diagnosis of CRC can improve the cure rate of surgical/endoscopic resection and, even when a cure is not possible, it may provide a better quality of life[21]. Greuter et al.[22] illustrate this matter, writing about the future impact of the Dutch CRC screening program. The Greuter et al. study estimated that the incidence rate of CRC should decrease by 31% and the mortality rate by 45% within 30 years due to screening.

As several different pathogenetic pathways are involved in the development of CRC and not all are well understood, Greuter et al. also evaluated the impact of the screening program in subgroups. When analysing CRCs derived solely from adenomas (i.e. excluding CRCs from the new and poorly understood serrated pathway), these numbers would be even more impressive (by 35% in incidence rate and by 47% in mortality rate). This suggests that a better understanding of the serrated pathway is needed for optimising CRC control by screening programs.

Extrapolating these findings to Australia's population, the CRC screening program has the potential to prevent CRC in almost 1 million people and, even when diagnosed, could prevent death by CRC in another 500,000 people due to early detection. Data from other countries, for instance North America, corroborate these expectations[23]. Nonetheless, despite the significant improvement in reducing the incidence of CRC through globally accepted colonoscopy screening programs, CRC is still one of the three most common cancers. This is of concern especially in Japan, because an increasing incidence in the Japanese population contrasts with the stable or decreasing trend in Western countries[24]. There is definitely room for improvement in the early detection and treatment of CRC in both the West and the East.

1.1.2 Detection of colorectal polyps and colorectal cancer

The screening programs were initially designed to detect and remove conventional adenomas, which had been considered the sole precursor of CRC through the classic adenoma-adenocarcinoma pathway[6]. However with the introduction of the serrated pathway, the different micro and macroscopic features of each pathway became important for an effective CRC screening. The following subsections will elaborate on features that have been associated with CRC screening and polyp detection during colonoscopy.

Histology of pre-malignant polyps. Conventional adenomas can be further divided into three types: tubular adenomas, tubulovillous adenomas and villous adenomas. After initial success in decreasing CRC incidence with these programs, the fact that some colorectal adenocarcinomas still appeared despite the removal of conventional adenomas led the scientific community to focus on other lesions that could be leading to these 'missed' CRCs.

With further investigation, the serrated pathway was found to be another major cause of colonic adenocarcinoma, second to that of the adenomatous pathway. The three subtypes of polyps that are recognized within the serrated polyp nomenclature then became the focus of gastrointestinal research. Serrated polyp subtypes are:

- hyperplastic polyp (HP)

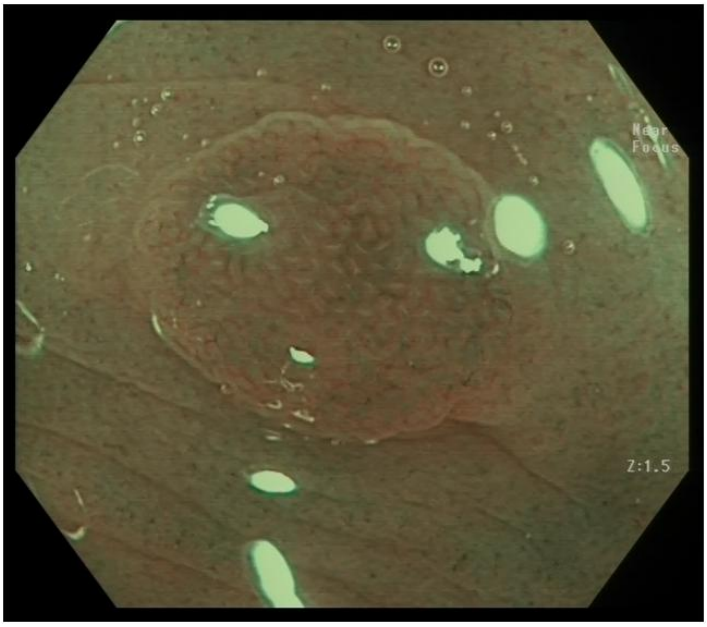


Figure 1.2 **HP on NBI and magnification. Classic features such as pale colour, thin white pit pattern and regular borders can be identified in this photo. (Original photograph, Leonardo Zorrón Cheng Tao Pu and Rajvinder Singh)**

- sessile serrated adenoma/polyp (SSA/P)

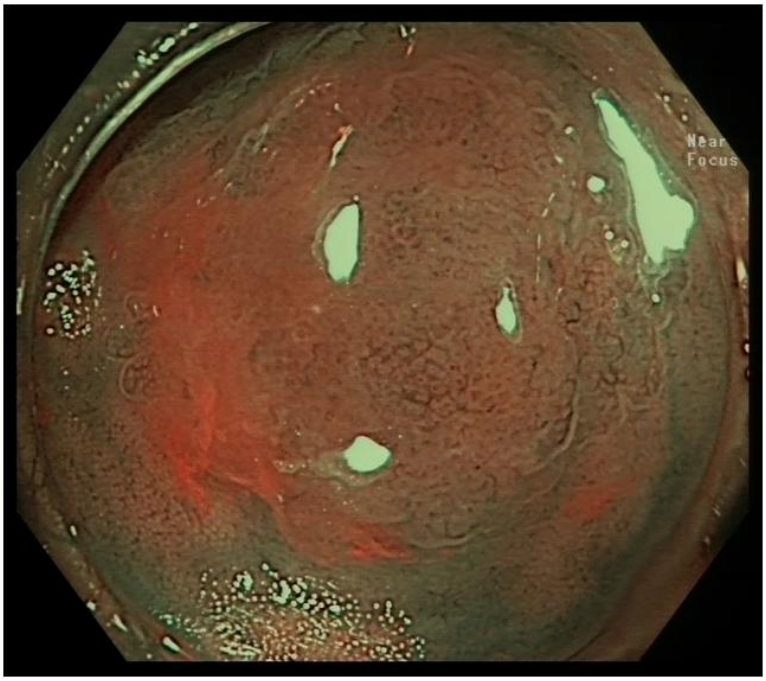


Figure 1.3 **SSA/P on NBI and near focus. Classic features such as mucous cap, varicose microvascular vessels, open pit pattern and irregular and inconspicuous borders can be identified in this photo. (Original photograph, Leonardo Zorrón Cheng Tao Pu and Rajvinder Singh)**

- traditional serrated adenoma (TSA)

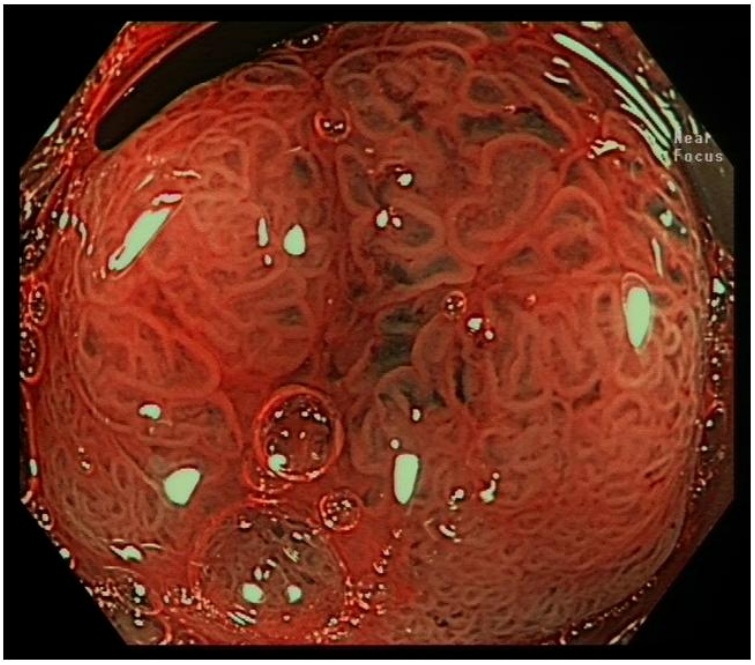


Figure 1.4 **TSA on NBI and near focus. Features identified in this photo such as dark colour, villi, elongated pit pattern and dense capillary network is also often found in villous and tubulovillous adenomas. (Original photograph, Leonardo Zorrón Cheng Tao Pu and Rajvinder Singh)**

New endoscopic technologies with better image resolution and assets that allow a more detailed analysis of colorectal lesions (e.g. chromoendoscopy and magnification) have aided in identifying the differences among serrated polyps, especially between HPs and SSA/Ps, which are quite similar both macroscopically and microscopically.

While a HP is considered a benign lesion when smaller than 5 mm and restricted to the rectosigmoid region[25], SSA/Ps have been shown in the last few years to contribute to up to 30% of CRCs, although their occurrence is low (4.5%)[26]. In Japan, Kawasaki et al.[27] detailed the epidemiology of colorectal polyps and found a 1.25% occurrence of SSA/Ps, much lower than what has been described in western countries. The discrepancy between the prevalence of SSA/Ps and their share of the responsibility for CRC may be explained by the nature of the serrated pathway, which seems to present a greater risk for the development of CRC than the traditional adenoma-carcinoma pathway[28]. This may be due to more aggressive behaviour and rapid progression from dysplasia to CRC[29]. However, it is possible that difficulties in actually detecting the lesion during colonoscopy explain their high contribution to CRC.

Sessile serrated adenoma/polyps are a relatively newly recognised polyp that not all endoscopists are aware of. In addition, even when the endoscopist is aware of SSA/P's existence, detection might be troublesome because of its inconspicuous features. Therefore, the identification and resection of SSA/Ps may be the next step towards improving the efficacy of screening programs, especially the prevention of interval CRC, that is a CRC diagnosed before the next scheduled colonoscopy as per the relevant gastrointestinal society's guidelines.

Factors associated with detection of colorectal polyps. In order to partially explain the variability in the reported prevalence of colorectal lesions, several factors must be considered. Apart from the population in which they were evaluated and the histopathological criteria, other factors can impact the number of polyps found. Therefore, caution is warranted when looking at reported prevalence in all forms of scientific publication.

Polyp location. The location of the polyp is one factor that may affect the reported epidemiology as location may be unevenly correlated with advanced histology and interval CRC. Right colon colorectal lesions are more associated with high grade dysplasia (HGD) and SSA/P histology than left colon colorectal lesions[30]. In keeping with this, more interval CRCs arise from the right colon and are associated with mutations found in the serrated pathway[31].

These interval cancers tend to behave more aggressively[32], and the majority of them are believed to develop from missed lesions[33]. Such missed lesions may correspond to either unrecognised polyps or polyps found but considered to be benign. It is possible that these lesions are related to SSA/P histology due to their subtle characteristics. In a way, the role of SSA/Ps in the development of CRC may have been 'enlarged' by the systematic removal of conventional adenomas in the last decades. On the other hand, it may have been 'shrunk' with increased awareness and systematic removal of SSA/Ps.

Colonoscopy indication. In addition, the reason behind the procedure affects the number of polyps found. Kahi et al.[34] have shown that patients under surveillance due to previous polyps have a higher adenoma detection rate (ADR) than patients simply having screening colonoscopies, and that patients submitted to diagnostic exams have the lowest ADR amongst the three.

Technology. ADR is also influenced by the use of high definition scopes, amounting to an impact of 3.5% more colonoscopies that identify at least one adenoma[35]. Some simple devices such as caps on the tip of the scope, have shown promising results towards a better polyp detection rate[36-38], most probably related to a better evaluation behind colonic folds. However, image enhancing endoscopy (IEE) techniques such as dye chromoendoscopy and virtual chromoendoscopy have produced conflicting results[39-42].

The endoscopist. In regard to the quality of colonoscopies, some metrics are commonly used for evaluating the efficacy of the endoscopist, such as adenoma detection rate (ADR), caecal intubation rate and compliance with the recommended surveillance intervals. The recommended minimum ADR, caecal intubation rate and compliance with the recommended surveillance intervals in the United States of America are 25% (20% for females and 30% for males), 90% (95% for screening patients) and 90% respectively[43]. In Australia, similar numbers are employed by the Gastroenterological Society of Australia. However, these rates may be subject to change due to increasing detection of adenomatous polyps in the last few

years. In some studies, ADR reaches up to 60% in the target screening population of over 50 years old[26].

Environmental factors. Some environmental factors have also been associated with the higher prevalence of CRC, and due to inductive logic, can be also associated with an increased prevalence of polyps. For instance, smoking has been associated with both[44,45]. Some indicators of a healthy lifestyle were associated with a lower risk of developing CRC in a large European cohort of more than 500,000 people[45]. The research analysed the impact of: overweight and obesity (body mass index $\geq$ 25 kg/m^2); physical activity (based on metabolic equivalent of task); smoking (current); alcohol consumption (men > 24 g per day and women > 12 g per day) and diet quality (based on country-specific validated dietary questionnaires) in the incidence of CRC. The study did not find statistical significance for isolated factors but identified an overall contribution towards lesser CRC incidence with a healthier lifestyle.

Diet has been associated with the development of colorectal lesions, especially in the West. The westernised diet is commonly described as high in fat, high in red meat and low in fibre. The most important aspect of diet in regard to CRC is not about what is absorbed. Rather, the faecal residuals are what have been described as contributors to CRC due to the interaction with the microbiota and consequent production of metabolites.

Westernised diets are associated with decreased butyrate and increased bile secretion (and thus increased secondary biliary acids) in stools. A high saturated fat diet has been associated with adenomas with high grade dysplasia in mice[46]. In clinical trials, the consumption of a westernised diet has been shown to have a role in the development of CRC. In a study by Le Marchand[47] it was discovered that there was an increase in the incidence of CRC in first generation Japanese descendants born overseas. The correlation was more significant in those who already had a familiar history of colorectal cancer, hence a genetic predisposition.

Bowel preparation. The adequacy of bowel preparation, which affects how clearly one can evaluate the colonic mucosa, also contributes to better detection and proper removal of colorectal lesions. Studies have consistently demonstrated a correlation between good cleansing of the bowel and a better detection of colorectal lesions and thus a more effective prevention of CRC[48,49]. For this evaluation a well-known and reliable score system was developed in Boston (United States of America), the Boston bowel preparation scale – BBPS[50].

The BBPS divides the large bowel into three parts (right colon, transverse and right colon), and scores them between 0 and 3 points. The score increases as a more proper bowel cleanse is identified. Hence, an optimal bowel preparation would score 9 points whereas a colon with solid fecal residues in the three bowel segments would score 0 points. Although Lai et al.[50] initially found that a score of 5 or more points is correlated with a better detection of colorectal polyps, some later studies associated better ADRs with BBPS of 6 or higher points and a segmental BBPS of 2 or higher points per segment.

1.2 Secondary and tertiary prevention of colorectal cancer

Although image enhancing endoscopy (IEE) technologies have proven to be effective in identifying and discriminating conventional adenomas from other colorectal lesions, the distinction of SSA/Ps from HPs has been more challenging. A recent meta-analysis showed that despite promising results with narrow band imaging (NBI), a technology from the Olympus company, more data are needed to confirm the use of IEE as a useful tool in order to detect SSA/Ps[51].

The incorporation of new IEE and the promising results of NBI has also been mentioned in the American Society for Gastrointestinal Endoscopy (ASGE) Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) program[3]. The importance of identifying precancerous polyps and removing them properly is directly related to the prevention of CRC. Consequently, the higher the detection rates of these polyps, the better the outcomes for the patient[52].

1.2.1 Characterisation of colorectal lesions

Several classifications have tried to use IEE in order to properly identify SSA/Ps with variable results and have been the focus of many studies in the past few years. The reason for developing an optimal classification system is the need to reduce unnecessary removal of benign lesions. The unnecessary removal and the histopathological analysis of benign colorectal lesions wastes resources. Moreover, the disadvantage removing benign polyps may exacerbate and outweigh the small complication rate that is intrinsic to colonoscopic procedures such as polypectomies and biopsies.

The use of NBI has been studied by several endoscopy experts and several classifications have been proposed including:

- Sano
- Modified Sano’s (MS)
- Hiroshima
- Japan NBI expert team (JNET)
- Showa
- Jikei
- NBI international colorectal endoscopic (NICE)
- workgroup serrated polyps and polyposis (WASP).

Overall, the classifications show similar levels of accuracy, but one has provided accuracy measures that surpass the threshold proposed by the ASGE and can also predict SSA/Ps[53,54], namely the Modified Sano's classification.

Described for the first time in 2013[55], MS is the most effective method for the differentiation of colorectal lesions. The MS classification in a randomised controlled trial demonstrated better diagnostic accuracy when compared to the NICE classification for differentiating neoplastic from non-neoplastic polyps with a sensitivity of 98.9%, specificity of 85.7%, positive predictive value of 98.2% and negative predictive value of 90.9%[53]. The accuracy was also significantly better when judging endoscopically resectable lesions. Moreover, comparing the results with the data from Ijspeert et al.[56], MS classification shows a slightly better result than the WASP classification. However, NICE is still one of the most widely used classifications in the West, probably due to its simplicity and ease of use. MS classification is divided into 5 types (I, IIo, II, IIIA and IIIB) while NICE is divided into 3 (1, 2 and 3).

Although many classifications have been created, there is still a highly variable performance when endoscopists predict histology of colorectal lesions in real-time. In studies from expert/academic centres, an accuracy or AUC of over 90% is often found when utilising endoscopic classifications based on NBI[57-59]. Nevertheless, for community-based endoscopists, the results are often suboptimal[60,61]. Suboptimal results for characterising colorectal lesions can be addressed with online or on-site training, boosting accuracy[62-65]. However, it appears that continuing education is required in order to sustain optimal results[66], which can be an issue in non-academic centres. Hence, despite all advances in endoscopic imaging, the excellent outcomes obtained in research centres are not widely reproducible as expertise is needed to achieve high accuracy.

Artificial intelligence. According to the *Oxford Dictionary*, artificial intelligence is a broad term used when computer systems are used for performing tasks for which human intellect would be required (e.g. visual perception and decision-making). This field has been rapidly progressing in the past few decades and has gained particular traction in medicine[67].

Computer-aided diagnosis, a branch of artificial intelligence, holds the potential to address suboptimal diagnostic performance. Several specialties within medicine, including gastroenterology, have been studying and achieving good results when using CAD systems[68-75]. As a consequence, CAD systems are being developed and can potentially lend augmented expertise to any endoscopist.

CAD has been developed and tested within the endoscopy field on the endocytoscopy system and has shown better accuracy for predicting the histology of polyps than non-expert endoscopists, with results similar to experts[76,77]. CAD has also been tested using NBI, and achieved similar results[78,79]. The major issue with these past studies is the inclusion of SSA/Ps in the non-neoplastic group. As the serrated pathway gains importance, development of a CAD that is able to differentiate benign and pre-malignant serrated colorectal lesions is paramount.

1.2.2 Minimally invasive treatment for colorectal polyps and early colorectal cancer

There are four major techniques for endoscopic resection of colorectal lesions:

- forceps (or excisional biopsy)

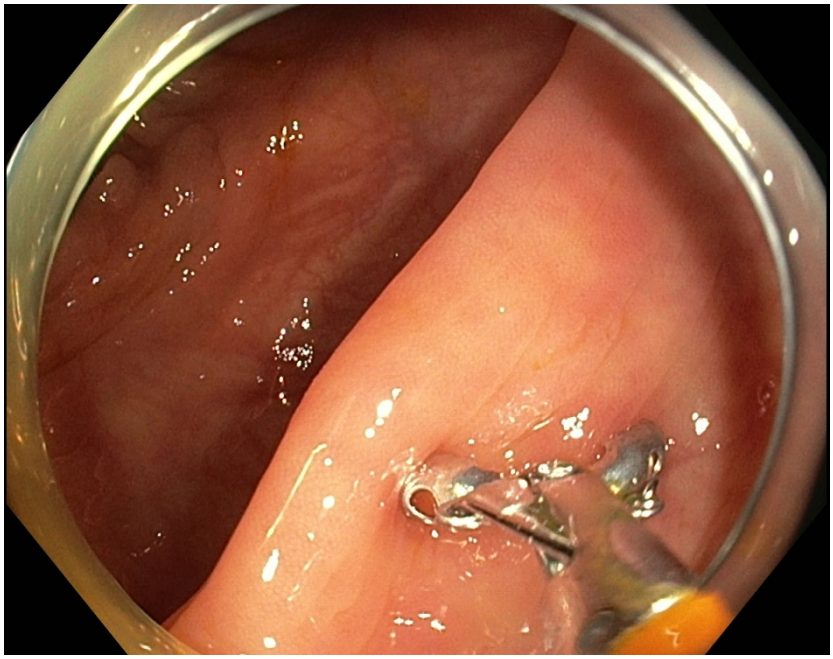


Figure 1.5 **Cold forceps being used for a sessile polyp in the colon (in progress). Technique falling in disuse in favour of cold snare resection. When used, should be restricted to diminutive lesions (<5 mm). (Original photograph, Kun Cheong Choi and Rajvinder Singh)**

- snare

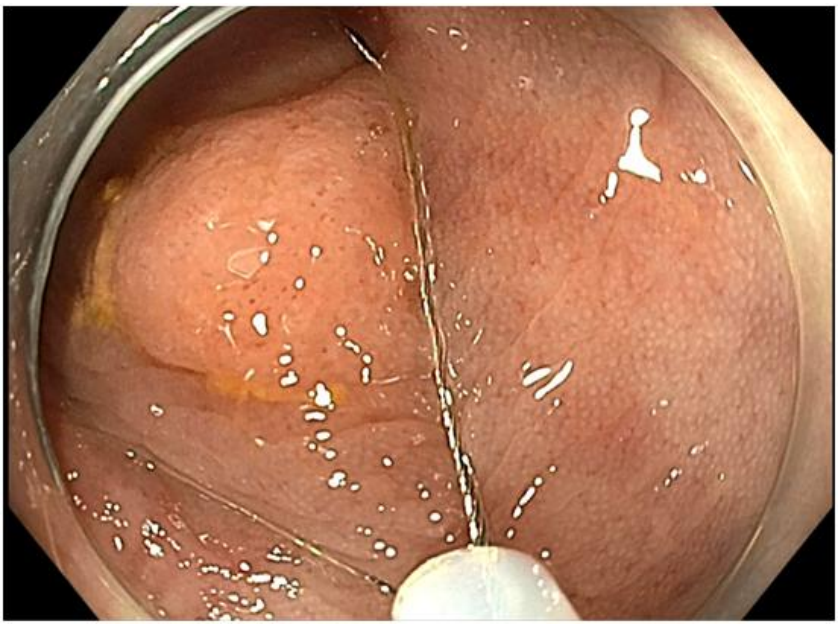


Figure 1.6 **Cold snare resection of a sessile polyp in the colon (pre-resection). Commonly, small lesions (<10 mm) are treated with this technique. (Original photograph, Leonardo Zorrón Cheng Tao Pu and Rajvinder Singh)**

- endoscopic mucosal resection (EMR)

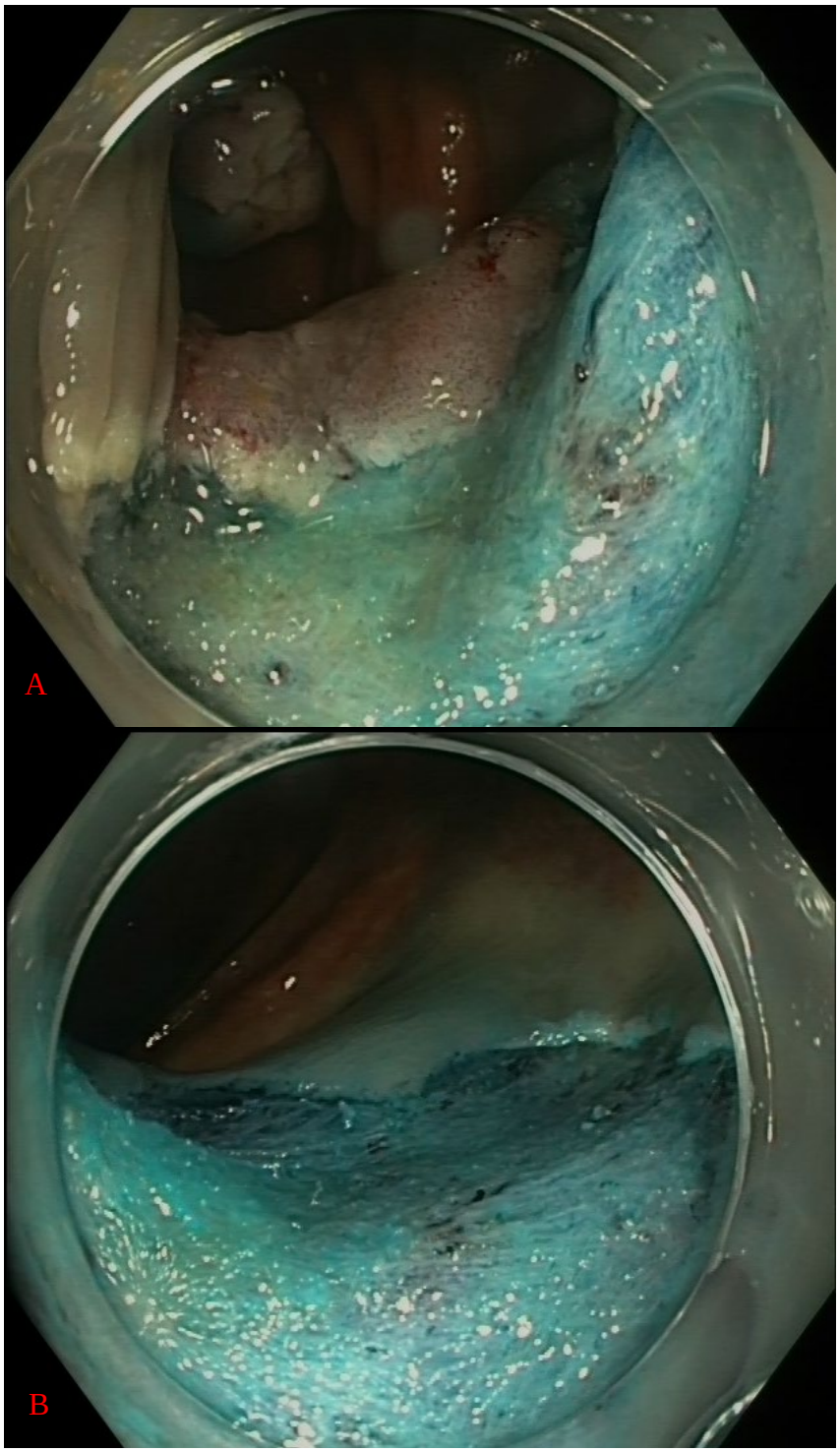


Figure 1.7 **Piecemeal EMR of a large lateral spreading tumour in the distal colon (A - in progress; B - finalised). This type of resection is common for large lesions. (Original photograph, Leonardo Zorrón Cheng Tao Pu and Rajvinder Singh)**

- endoscopic submucosal dissection (ESD)

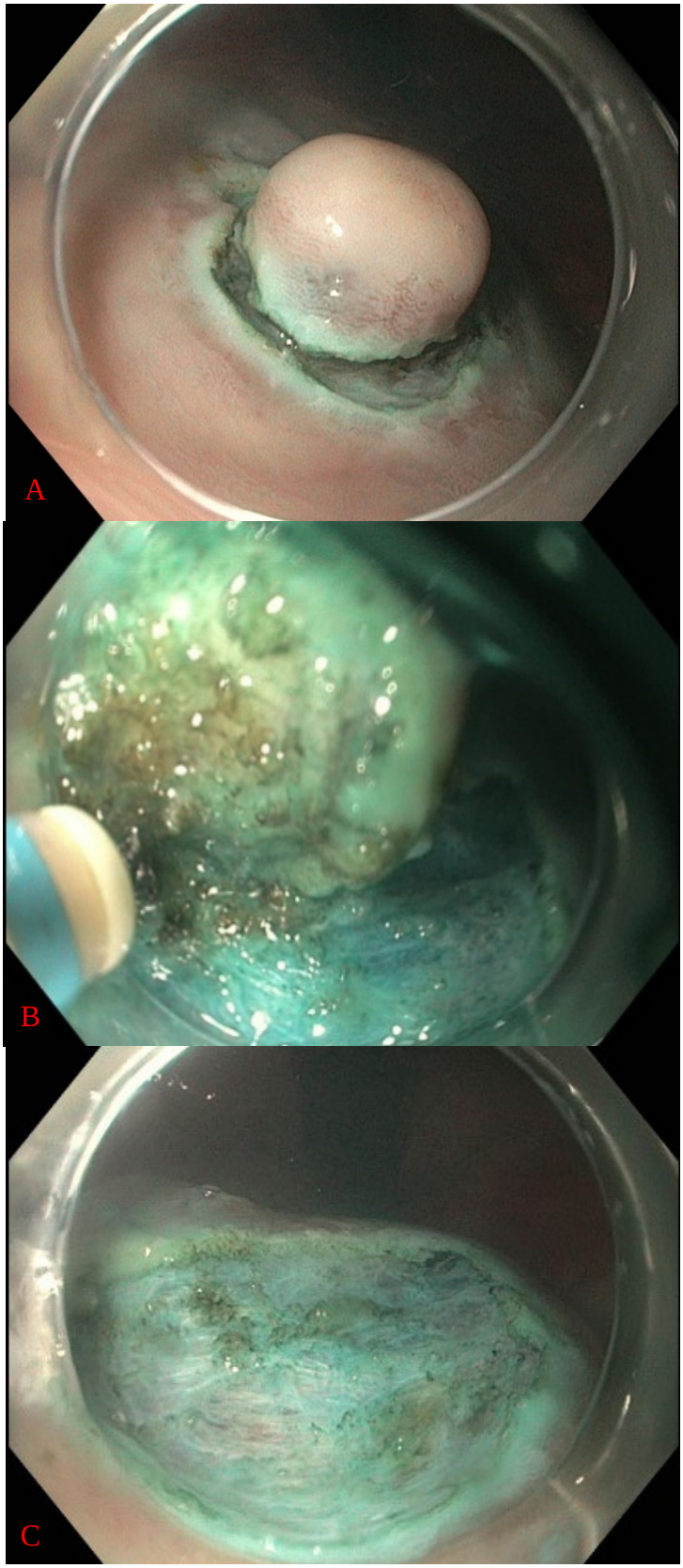


Figure 1.8 **ESD of a rectal neuroendocrine tumour. A) illustrates the end of the circumferential incision; B) shows the submucosal dissection step and C) corresponds to the colonic lining wound after the resection is finalised. This type of resection is also common for large lesions. (Original photograph, Leonardo Zorrón Cheng Tao Pu and Rajvinder Singh)**

The latter two commonly utilise electric currents. The first two can be further divided into 'hot' (when associated with an electric source) and 'cold' (without an electric source). For each modality, several options for accessories are available. If for any reason a colorectal lesion is not considered for resection due to deep invasion, an incisional biopsy with forceps is usually performed. The option for one over the other usually considers the size, location, predicted histology, depth of invasion and, ultimately, the endoscopist's experience.

The size cut-off for the division of small and large polyps is 10 mm. Flat lesions above that cut-off are called lateral spreading tumours (LSTs), which can be further subdivided into LST granular homogeneous (LST-G-H), LST granular nodular mixed (LST-G-M) and LST non-granular (LST-NG). Large polyps and small polyps with features that can complicate their excision, such as a previous biopsy or previous attempted resection, are also considered complex. For these lesions the suggested resection method is either ESD or EMR[80,81].

Apart from the globally accepted principle that all lesions should be resected with the margins carefully evaluated, the optimum resection method for complex lesions is still under debate[80, 81]. Studies in Japan emphasise the benefit of en bloc resections and consequently less recurrence for lesions > 20 mm, as well as deeper cuts with better deep margins, which is preferred in the East, especially in Japan. However, this type of resection has the highest adverse event rates among all endoscopic resection methods[24].

On the other hand, the EMR advocated by some centres in the West, including Australia, is a more rapid and less invasive method with fewer complications[82,83]. The major issue about this technique is related to the completeness of the resection. If the colorectal lesion is too large to be resected in one piece, it is done in the so called 'piecemeal resection', which has been associated with a higher recurrence rate. Furthermore, the specimens resected with EMR commonly have a shallower cut and therefore a thinner deep margin, which may be associated with fewer complications when compared to ESD[84].

There are two factors to be considered in relation to colorectal lesions in the right colon. First, they are more difficult to operate on with advanced endoscopic resection techniques (e.g. ESD). Second, the right colon has a thinner wall. Therefore, in the resection of a sessile polyp for instance, the use of electrical currents should be carefully considered to avoid complications such as post-polypectomy syndrome (persistent abdominal pain, fever and leucocytosis without frank perforation after polypectomy).

Additionally, other issues must be considered in the decision-making process for treating a colorectal lesion. The histology of the lesion, for instance, is important for a range of reasons. Benign lesions that may resemble a polyp (e.g. lipoma) should not be excised. If an invasive cancer is found, it should be biopsied only and the patient sent to surgery. Therefore, the importance of an accurate endoscopic diagnostic method for predicting histology before the

resection of the colorectal lesion is paramount. However, it does not exempt the resection and pathologic evaluation of the resected specimen.

Early CRC has been successfully resected with advanced endoscopic resection techniques (EMR and ESD), but according to the Japanese Society of Gastroenterology should be employed only for lesions restricted to 1000 micrometres of depth[24]. Herein lies the importance of IEE for determining the depth commitment of the colorectal lesion.

The endoscopist's expertise in one or other methods is of the utmost importance for a successful resection. It is unanimous in conference meetings that if someone masters an endoscopic resection technique that can be applied to a certain lesion, this technique should be the one used. This is also true regarding detection, and the endoscopist/Endoscopy Centre expertise is important[85].

Finally, after resecting the lesion a follow up of the resected area must be performed for surveillance of recurrence, in addition to the surveillance for metachronous colorectal lesions. A colonoscopy following EMR/ESD is usually performed after four to six months to check for any signs of recurrence, when a biopsy is made from the scar. The predictors for the likelihood of recurrence have been reported and involve the size of the resected lesion, the presence of bleeding during the procedure, and HGD. These were independent associate factors in a multivariate analysis on more than 1,000 lesions[86]. The features of the scar and their correlation with negative endoscopic prediction have been investigated further and have shown promising results in a recent study by Desomer et al.[87].

This thesis by publication has been organised with chapters consisting of submitted or accepted/published papers. Chapter 2 consists of a narrative review focused on SSA/P and Chapters 3 to 11 offer original papers, in logical order from primary to tertiary prevention.

1.3 Research aims of this thesis

The intention of this PhD was to investigate cohorts of patients in Australia and Japan, seeking to close gaps in the literature surrounding primary, secondary and tertiary prevention of CRC. The variability of evidence, clinical practice and culture between the East and West presented a challenge and at the same time an opportunity for this joint PhD program between Australia and Japan.

1.4 Organisation of the thesis

The remaining chapters of this thesis are ordered as follows:

Chapter 2 focusses on SSA/Ps which represent the more recently uncovered serrated pathway to CRC. This narrative review explores SSA/Ps from their definition to detection and treatment, and highlights the gaps in knowledge pertaining these colorectal lesions.

The paper derived from the examination of the literature before engaging in the original research for the PhD and included in Chapter 2 was published in *World Journal of Gastroenterology* in 2016 as *Sessile serrated adenoma/polyps: Where are we at in 2016?*

In **Chapter 3**, factors (e.g. diet and lifestyle) were prospectively investigated for their association with colorectal lesions in Australia. As data on CRC-related factors in the literature are highly variable and data from Australia are scarce, the results of this study should contribute to the body of knowledge in the field.

The accepted paper included in Chapter 3 is to be published in *Nagoya Journal of Medical Science* in 2020 as *Different factors are associated with conventional adenoma and serrated colorectal neoplasia.*

Chapter 4 describes a cohort of surgeons and gastroenterologists performing colonoscopies in a South Australian hospital who were retrospectively analysed, focusing on the effect of scheduling and specialty on the detection of colorectal lesions. Around the world, medical practice and training are diverse and there are few studies looking at these two factors in Australia. The results described in this chapter are expected to help guide the improvement in detection of colorectal lesions.

The paper included in Chapter 4 was published in *Journal of Gastroenterology and Hepatology* in 2018 as *Effect of time of day and specialty on polyp detection rates in Australia.*

Chapter 5 describes how a cohort of patients undergoing colonoscopies at the Lyell McEwin Hospital (South Australia) was retrospectively assessed for determining detection quotients that could potentially allow the use of the less cumbersome polyp detection rate as a surrogate for adenoma and SSA/P detection rates. The study discussed in Chapter 5 compared and added findings of an Australian cohort to the body of knowledge produced from similar studies performed in other countries.

The accepted paper included in Chapter 5 is to be published in *Gastrointestinal Tumors* in 2020 as *Polyp detection rate as a surrogate for adenoma and sessile serrated adenoma/polyp detection rates.*

Chapter 6 provides a comparison of the most used versus the most comprehensive endoscopic classification for the prediction of histology in the Western world. This was a randomised study searching for the best classification among the NICE and MS classifications, excluding

the differentiation of SSA/Ps. This study was further complemented by another study including SSA/Ps.

The paper included in Chapter 6 was published in *World Journal of Gastrointestinal Endoscopy* in 2018 as *Randomised controlled trial comparing modified Sano's and narrow band imaging international colorectal endoscopic classifications for colorectal lesions.*

In **Chapter 7**, the three most comprehensive and/or utilised classifications in the world are compared: NICE plus WASP, JNET plus WASP and MS. The combination of the NICE and JNET classifications with WASP enabled the diagnosis of SSA/P, hence a more adequate comparison was achieved. The study sought to determine which would be the most accurate classification with the capability of identifying SSA/Ps.

The paper included in Chapter 7 has been submitted to and is currently under peer review in *Surgical Endoscopy* as *Comparison of different virtual chromoendoscopy classification systems for the characterisation of colorectal neoplasia.*

In **Chapter 8**, an artificial intelligence system based on convolutional neural networks was trained using the MS classification for the prediction of colorectal lesion histology. The study successfully created a CAD trained with NBI images that was able to predict ex-vivo both NBI and BLI images with results similar to experts.

The paper included in Chapter 8 has been submitted to and is currently undergoing peer review for *Gastrointestinal Endoscopy* as *Computer aided diagnosis for characterisation of colorectal lesions: a comprehensive software including serrated lesions.*

Chapter 9 reports on the bacterial profiles of early and invasive CRC. Knowing the different bacterial profiles associated with each CRC type has the potential to aid in diagnosis and treatment. This study was focused on investigating such differences, concentrating on the *Fusobacterium* genus presence on the CRC mucous cap.

The paper included in Chapter 9 was published in *Journal of Gastroenterology and Hepatology* in 2019 as *Microbiota profile is markedly different for early and invasive colorectal cancer; and is consistent throughout the colon.*

Chapter 10 reports on the evaluation of the resection of early CRC through ESD. More specifically, the study investigated the evolution of colorectal ESD trainees over time in regard to safety and efficacy in performing this elaborate procedure. Due to the difficulty of the ESD procedure, especially when performed in the colon, large studies are rare in the literature.

The paper included in Chapter 10 has been accepted for publication by *JGH Open* as *Learning curve for mastery of colorectal endoscopic submucosal dissection: perspectives from a large Japanese cohort.*

In **Chapter 11**, an endoscopic classification for prediction of recurrence on surveillance after endoscopic resection is proposed. Currently, an endoscopic classification for such end lacks. This study conceived and validated the NBI-SCAR classification in different countries. It is expected that if our results are confirmed in future studies, this could become a standard form of endoscopic evaluation for post-endoscopic resection scars.

The paper included in Chapter 11 was published in *Gastrointestinal Endoscopy* in 2019 as *Narrow band imaging for scar (NBI-SCAR) classification: from conception to multicenter validation.* A flowchart is supplied below to facilitate the understanding of this thesis organisation.

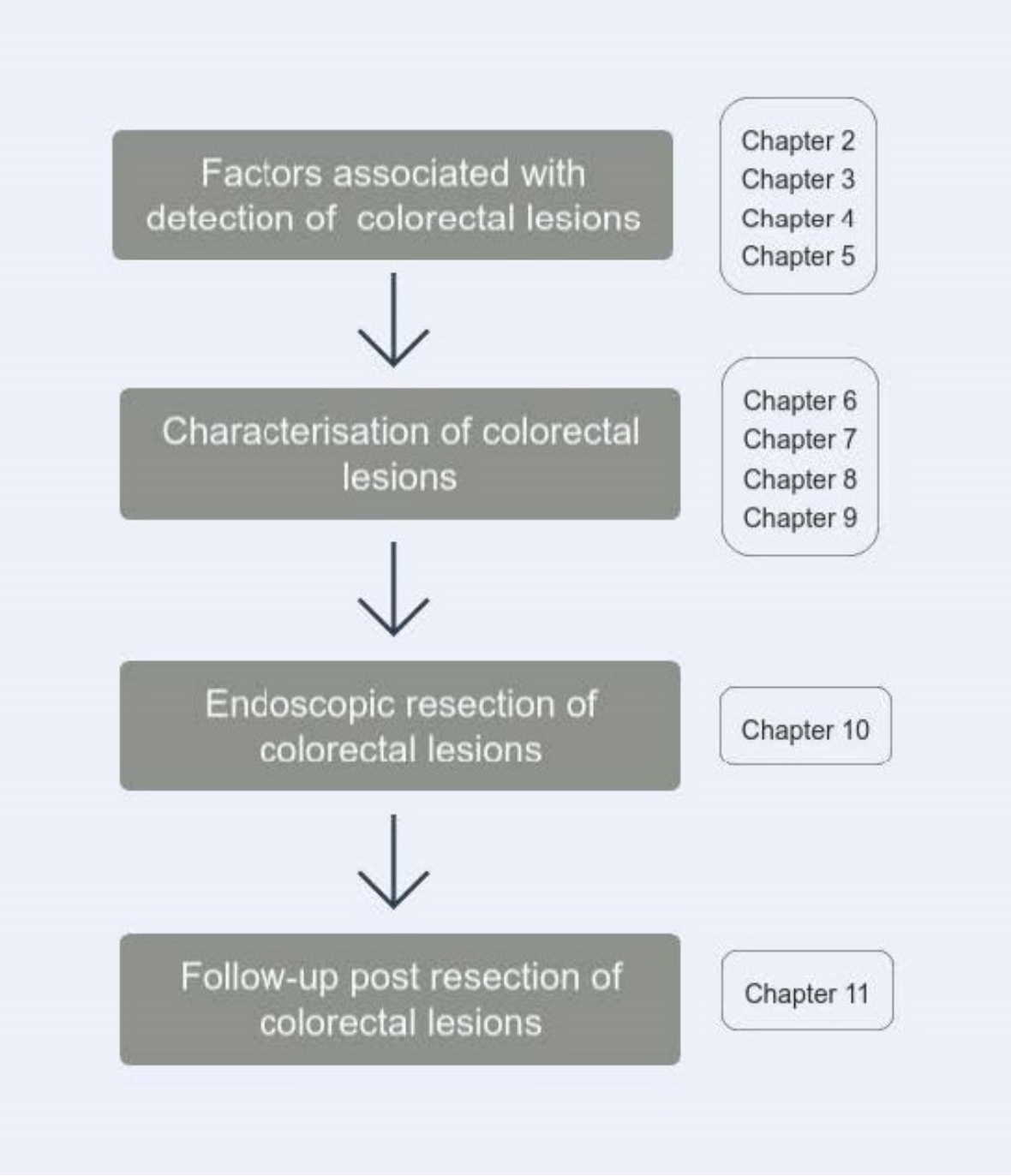


Figure 1.9 Thesis flowchart

1.5 References for Chapter 1

1. Australian Institute of Health and Welfare 2019. Cancer data in Australia. Cat. no. CAN 122. Canberra: AIHW. Viewed 30 November 2019, https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia

2. National Cancer Center Japan. Cancer Registry and Statistics. Cancer Information Service. 2018. Viewed 30 November 2019, https://ganjoho.jp/data/reg_stat/statistics/brochure/2018/cancer_statistics_2018_fig_E.pdf

3. Abu Dayyeh BK, Thosani N, Konda V, Wallace MB, Rex DK, Chauhan SS, et al. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting real-time endoscopic assessment of the histology of diminutive colorectal polyps. Gastrointestinal Endoscopy. 2015 3//;81(3):502.e1-.e16. DOI: http://dx.doi.org/10.1016/j.gie.2014.12.022.

4. Bettington M, Walker N, Clouston A, Brown I, Leggett B, Whitehall V. The serrated pathway to colorectal carcinoma: current concepts and challenges. Histopathology. 2013;62(3):367-86. DOI: 10.1111/his.12055.

5. Terada T. Histopathologic study of the rectum in 1,464 consecutive rectal specimens in a single Japanese hospital: II. malignant lesions. International Journal of Clinical and Experimental Pathology. 2013;6(3):385-94.

6. Pino MS, Chung DC. The chromosomal instability pathway in colon cancer. Gastroenterology. 2010 Jun;138(6):2059-72. DOI: 10.1053/j.gastro.2009.12.065.

7. Pang XL, Li QX, Ma ZP, Shi Y, Ma YQ, Li XX, et al. Association between clinicopathological features and survival in patients with primary and paired metastatic colorectal cancer and KRAS mutation. OncoTargets and Therapy. 2017;10:2645-54. DOI: 10.2147/ott.S133203.

8. Tsai JH, Liau JY, Lin YL, Tseng LH, Lin LI, Yeh KH, et al. Frequent BRAF mutation in early-onset colorectal cancer in Taiwan: association with distinct clinicopathological and molecular features and poor clinical outcome. J Clin Pathol. 2016 Apr;69(4):319-25. DOI: 10.1136/jclinpath-2015-203335.

9. Carr NJ, Mahajan H, Tan KL, Hawkins NJ, Ward RL. Serrated and non-serrated polyps of the colorectum: their prevalence in an unselected case series and correlation of BRAF mutation analysis with the diagnosis of sessile serrated adenoma. J Clin Pathol. 2009;62. DOI: 10.1136/jcp.2008.061960.

10. Gill P, Rafferty H, Munday D, Bailey A, Wang LM, East JE, et al. Proximal colon cancer and serrated adenomas - hunting the missing 10%. Clinical Medicine (London, England). 2013 Dec;13(6):557-61. DOI: 10.7861/clinmedicine.13-6-557.

11. Kahi CJ, Hewett DG, Norton DL, Eckert GJ, Rex DK. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. Clin Gastroenterol Hepatol. 2011 Jan;9(1):42-6. DOI: 10.1016/j.cgh.2010.09.013.

12. Fernando WC, Miranda MS, Worthley DL, Togashi K, Watters DJ, Leggett BA, et al. The CIMP phenotype in BRAF mutant serrated polyps from a prospective colonoscopy patient cohort. Gastroenterology Research and Practice. 2014;2014:374926. DOI: 10.1155/2014/374926.

13. Snover D, Ahnen D, Burt R, Odze R. WHO classification of tumours. Pathology and genetics. Tumours of Digestive System. Berlin: Springer; 2010.

14. Shida Y, Ichikawa K, Fujimori T, Fujimori Y, Tomita S, Fujii T, et al. Differentiation between sessile serrated adenoma/polyp and non-sessile serrated adenoma/polyp in large hyper plastic polyp: a Japanese collaborative study. Mol Clin Oncol. 2013 Jan;1(1):53-8. DOI: 10.3892/mco.2012.20.

15. World Health Organization. Cancer screening 2019. Viewed 15/11/2019, https://www.who.int/cancer/prevention/diagnosis-screening/screening/en/

16. Wilson JMG, Jugner G. Principles and practice of screening for disease. Public Health Papers. 1968;34:168.

17. National Center for Biotechnology Information (NCBI) Bookshelf. InformedHealth.org [Internet]. Benefits and risks of screening tests 2019. Viewed 15/11/2019, https://www.ncbi.nlm.nih.gov/books/NBK279418/

18. Altobelli E, Lattanzi A, Paduano R, Varassi G, di Orio F. Colorectal cancer prevention in Europe: burden of disease and status of screening programs. Preventive Medicine. 2014 May;62:132-41. DOI: 10.1016/j.ypmed.2014.02.010.

19. Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, et al. Colorectal cancer screening: a global overview of existing programmes. Gut. 2015 Oct;64(10):1637-49. DOI: 10.1136/gutjnl-2014-309086.

20. van Rossum LG, van Rijn AF, Verbeek AL, van Oijen MG, Laheij RJ, Fockens P, et al. Colorectal cancer screening comparing no screening, immunochemical and guaiac fecal occult blood tests: a cost-effectiveness analysis. International Journal of Cancer. 2011 Apr 15;128(8):1908-17. DOI: 10.1002/ijc.25530.

21. Reyes ME, Ye Y, Zhou Y, Liang A, Kopetz S, Rodriquez MA, et al. Predictors of health-related quality of life and association with survival may identify colorectal cancer patients at high risk of poor prognosis. Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation. 2016 Aug 4. DOI: 10.1007/s11136-016-1381-8.

22. Greuter MJ, Demirel E, Lew JB, Berkhof J, Xu XM, Canfell K, et al. Long-term impact of the Dutch colorectal cancer screening program on cancer incidence and mortality-model-based exploration of the serrated pathway. Cancer Epidemiol Biomarkers Prev. 2016 Jan;25(1):135-44. DOI: 10.1158/1055-9965.epi-15-0592.

23. Nishihara R, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. New England Journal of Medicine. 2013;369(12):1095-105. DOI: doi:10.1056/NEJMoa1301969.

24. Tanaka S, Saitoh Y, Matsuda T, Igarashi M, Matsumoto T, Iwao Y, et al. Evidence-based clinical practice guidelines for management of colorectal polyps. Journal of Gastroenterology. 2015 Mar;50(3):252-60. DOI: 10.1007/s00535-014-1021-4.

25. Ponugoti P, Lin J, Odze R, Snover D, Kahi C, Rex DK. Prevalence of sessile serrated adenoma/polyp in hyperplastic-appearing diminutive rectosigmoid polyps. Gastrointest Endosc. 2017 Mar;85(3):622-7. DOI: 10.1016/j.gie.2016.10.022.

26. Laird-Fick HS, Chahal G, Olomu A, Gardiner J, Richard J, Dimitrov N. Colonic polyp histopathology and location in a community-based sample of older adults. BMC Gastroenterology. [journal paper]. 2016;16(1):1-7. DOI: 10.1186/s12876-016-0497-1.

27. Kawasaki K, Kurahara K, Yanai S, Oshiro Y, Yao T, Kobayashi H, et al. Colonoscopic features and malignant potential of sessile serrated adenomas: comparison with other serrated lesions and conventional adenomas. Colorectal Dis. 2016 Jan 19. DOI: 10.1111/codi.13276.

28. Erichsen R, Baron JA, Hamilton-Dutoit SJ, Snover DC, Torlakovic EE, Pedersen L, et al. Increased risk of colorectal cancer development among patients with serrated polyps. gastroenterology. 2016 4//;150(4):895-902.e5. DOI: http://dx.doi.org/10.1053/j.gastro.2015.11.046.

29. Bettington M, Walker N, Rosty C, Brown I, Clouston A, McKeone D, et al. Clinicopathological and molecular features of sessile serrated adenomas with dysplasia or carcinoma. Gut. 2015 Oct 15. DOI: 10.1136/gutjnl-2015-310456.

30. Yang JF, Tang S-J, Lash RH, Wu R, Yang Q. Anatomic distribution of sessile serrated adenoma/polyp with and without cytologic dysplasia. Archives of Pathology & Laboratory Medicine. 2015;139(3):388-93. DOI: doi:10.5858/arpa.2013-0523-OA.

31. Stoffel EM, Erichsen R, Frøslev T, Pedersen L, Vyberg M, Koeppe E, et al. Clinical and molecular characteristics of post-colonoscopy colorectal cancer: A population-based study. Gastroenterology. 2016. DOI: http://dx.doi.org/10.1053/j.gastro.2016.07.010.

32. Erichsen R, Stoffel EM, Sandler RS, Baron JA, Sørensen HT. Su1437 Prognosis of interval and sporadic colorectal cancer in Danish patients: a nationwide cohort study. Gastrointestinal Endoscopy. 2012 4//;75(4, Supplement):AB331. DOI: http://dx.doi.org/10.1016/j.gie.2012.03.862.

33. Robertson DJ, Lieberman DA, Winawer SJ, Ahnen DJ, Baron JA, Schatzkin A, et al. Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. Gut. 2014 Jun;63(6):949-56. DOI: 10.1136/gutjnl-2012-303796.

34. Kahi CJ, Vemulapalli KC, Johnson CS, Rex DK. Improving measurement of the adenoma detection rate and adenoma per colonoscopy quality metric: the Indiana University experience. Gastrointest Endosc. 2014 Mar;79(3):448-54. DOI: 10.1016/j.gie.2013.10.013.

35. Subramanian V, Mannath J, Hawkey CJ, Ragunath K. High definition colonoscopy vs. standard video endoscopy for the detection of colonic polyps: a meta-analysis. Endoscopy. 2011 Jun;43(6):499-505. DOI: 10.1055/s-0030-1256207.

36. Jian HX, Feng BC, Zhang Y, Qu JY, Li YY, Zuo XL. EndoCuff-assisted colonoscopy could improve adenoma detection rate: A meta-analysis of randomized controlled trials. Journal of Digestive Diseases. 2019 Aug 19. DOI: 10.1111/1751-2980.12814.

37. Nutalapati V, Kanakadandi V, Desai M, Olyaee M, Rastogi A. Cap-assisted colonoscopy: a meta-analysis of high-quality randomized controlled trials. Endosc Int Open. 2018 Oct;6(10):E1214-e23. DOI: 10.1055/a-0650-4258.

38. Facciorusso A, Triantafyllou K, Murad MH, Prokop LJ, Tziatzios G, Muscatiello N, et al. Compared abilities of endoscopic techniques to increase colon adenoma detection rates: a network meta-analysis. Clin Gastroenterol Hepatol. 2019 Nov;17(12):2439-54.e25. DOI: 10.1016/j.cgh.2018.11.058.

39. Singh R, Cheong KL, Zorron Cheng Tao Pu L, Mangira D, Koay DSC, Kee C, et al. Multicenter randomised controlled trial comparing the high definition white light endoscopy and the bright narrow band imaging for colon polyps. World Journal of Gastrointestinal Endoscopy. 2017 Jun 16;9(6):273-81. DOI: 10.4253/wjge.v9.i6.273.

40. Atkinson NSS, Ket S, Bassett P, Aponte D, De Aguiar S, Gupta N, et al. Narrow-band imaging for detection of neoplasia at colonoscopy: a meta-analysis of data from individual patients in randomized controlled trials. Gastroenterology. 2019 Aug;157(2):462-71. DOI: 10.1053/j.gastro.2019.04.014.

41. Repici A, Wallace MB, East JE, Sharma P, Ramirez FC, Bruining DH, et al. Efficacy of per-oral methylene blue formulation for screening colonoscopy. Gastroenterology. 2019 Jun;156(8):2198-207.e1. DOI: 10.1053/j.gastro.2019.02.001.

42. Aziz M, Desai M, Hassan S, Fatima R, Dasari CS, Chandrasekar VT, et al. Improving serrated adenoma detection rate in the colon by electronic chromoendoscopy and distal attachment: systematic review and meta-analysis. Gastrointest Endosc. 2019 Nov;90(5):721-31.e1. DOI: 10.1016/j.gie.2019.06.041.

43. Rex DK, Schoenfeld PS, Cohen J, Pike IM, Adler DG, Fennerty MB, et al. Quality indicators for colonoscopy. Gastrointestinal Endoscopy. 2015 1//;81(1):31-53. DOI: http://dx.doi.org/10.1016/j.gie.2014.07.058.

44. IJspeert JE, Bossuyt PM, Kuipers EJ, Stegeman I, de Wijkerslooth TR, Stoop EM, et al. Smoking status informs about the risk of advanced serrated polyps in a screening population. Endosc Int Open. 2016 Jan;4(1):E73-8. DOI: 10.1055/s-0034-1393361.

45. Aleksandrova K, Pischon T, Jenab M, Bueno-de-Mesquita HB, Fedirko V, Norat T, et al. Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. BMC medicine. 2014;12:168. DOI: 10.1186/s12916-014-0168-4.

46. Harris KL, Pulliam SR, Okoro E, Guo Z, Washington MK, Adunyah SE, et al. Western diet enhances benzo(a)pyrene-induced colon tumorigenesis in a polyposis in rat coli (PIRC) rat model of colon cancer. Oncotarget. 2016 May 17;7(20):28947-60. DOI: 10.18632/oncotarget.7901.

47. Marchand LL. Combined influence of genetic and dietary factors on colorectal cancer incidence in Japanese Americans. JNCI Monographs. 1999 December 1, 1999;1999(26):101-5.

48. Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, et al. Adenoma detection rate and risk of colorectal cancer and death. New England Journal of Medicine. 2014;370(14):1298-306. DOI: doi:10.1056/NEJMoa1309086.

49. Jain D, Momeni M, Krishnaiah M, Anand S, Singhal S. Importance of reporting segmental bowel preparation scores during colonoscopy in clinical practice. World Journal of Gastroenterology. 2015 Apr 7;21(13):3994-9. DOI: 10.3748/wjg.v21.i13.3994.

50. Lai EJ, Calderwood AH, Doros G, Fix OK, Jacobson BC. The Boston bowel preparation scale: a valid and reliable instrument for colonoscopy-oriented research. Gastrointest Endosc. 2009 Mar;69(3 Pt 2):620-5. DOI: 10.1016/j.gie.2008.05.057.

51. Parikh ND, Chaptini L, Njei B, Laine L. Diagnosis of sessile serrated adenomas/polyps with image-enhanced endoscopy: a systematic review and meta-analysis. Endoscopy. 2016 Aug;48(8):731-9. DOI: 10.1055/s-0042-107592.

52. Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, et al. Adenoma detection rate and risk of colorectal cancer and death. The New England Journal of Medicine. 2014 Apr 3;370(14):1298-306. DOI: 10.1056/NEJMoa1309086.

53. Yeap SP, Singh R, Ovenden A, Ruszkiewicz A, Lau JY, Rerknimitr R, et al. Sa1557 A randomised controlled trial comparing the modified sano's versus the nice classifications using narrow band imaging with near focus magnification in differentiating colorectal polyps. Gastrointestinal Endoscopy. 2015 5//;81(5, Supplement):AB259-AB60. DOI: http://dx.doi.org/10.1016/j.gie.2015.03.1346.

54. Kuruvilla N, Paramsothy R, Gill R, Selby WS, Remedios ML, Kaffes AJ. A prospective dual-center proof-of-principle study evaluating the incremental benefit of narrow-band imaging with a fixed zoom function in real-time prediction of polyp histology. Can we resect and discard? Gastrointest Endosc. 2015 Aug;82(2):362-9. DOI: 10.1016/j.gie.2015.01.014.

55. Singh R, Jayanna M, Navadgi S, Ruszkiewicz A, Saito Y, Uedo N. Narrow-band imaging with dual focus magnification in differentiating colorectal neoplasia. Digestive Endoscopy: Official Journal of the Japan Gastroenterological Endoscopy Society. 2013 May;25 Suppl 2:16-20. DOI: 10.1111/den.12075.

56. IJspeert JE, Bastiaansen BA, van Leerdam ME, Meijer GA, van Eeden S, Sanduleanu S, et al. Development and validation of the WASP classification system for optical diagnosis of adenomas, hyperplastic polyps and sessile serrated adenomas/polyps. Gut. 2016 Jun;65(6):963-70. DOI: 10.1136/gutjnl-2014-308411.

57. Iwatate M, Sano Y, Hattori S, Sano W, Hasuike N, Ikumoto T, et al. The addition of high magnifying endoscopy improves rates of high confidence optical diagnosis of colorectal polyps. Endosc Int Open. 2015 Apr;3(2):E140-5. DOI: 10.1055/s-0034-1391362.

58. Hayashi N, Tanaka S, Hewett DG, Kaltenbach TR, Sano Y, Ponchon T, et al. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the Narrow-Band Imaging International Colorectal Endoscopic (NICE) classification. Gastrointestinal Endoscopy.78(4):625-32. DOI: 10.1016/j.gie.2013.04.185.

59. Minoda Y, Ogino H, Chinen T, Ihara E, Haraguchi K, Akiho H, et al. Objective validity of the Japan narrow-band imaging expert team classification system for the differential diagnosis of colorectal polyps. Digestive Endoscopy.0(0). DOI: 10.1111/den.13393.

60. Rees CJ, Rajasekhar PT, Wilson A, Close H, Rutter MD, Saunders BP, et al. Narrow band imaging optical diagnosis of small colorectal polyps in routine clinical practice: the Detect Inspect Characterise Resect and Discard 2 (DISCARD 2) study. Gut. 2017 May;66(5):887-95. DOI: 10.1136/gutjnl-2015-310584.

61. Ladabaum U, Fioritto A, Mitani A, Desai M, Kim JP, Rex DK, et al. Real-time optical biopsy of colon polyps with narrow band imaging in community practice does not yet meet key thresholds for clinical decisions. Gastroenterology. 2013 Jan;144(1):81-91. DOI: 10.1053/j.gastro.2012.09.054.

62. Vleugels JLA, Dijkgraaf MGW, Hazewinkel Y, Wanders LK, Fockens P, Dekker E. Effects of training and feedback on accuracy of predicting rectosigmoid neoplastic lesions and selection of surveillance intervals by endoscopists performing optical diagnosis of diminutive polyps. Gastroenterology. 2018 May;154(6):1682-93.e1. DOI: 10.1053/j.gastro.2018.01.063.

63. Smith SCL, Saltzman J, Shivaji UN, Lethebe BC, Cannatelli R, Ghosh S, et al. Randomized controlled study of the prediction of diminutive/small colorectal polyp histology using didactic versus computer-based self-learning module in gastroenterology trainees. Digestive Endoscopy: Official Journal of the Japan Gastroenterological Endoscopy Society. 2019 Sep;31(5):535-43. DOI: 10.1111/den.13389.

64. Basford P, Longcroft-Wheaton G, Higashi R, Uraoka T, Bhandari P. Colonic lesion characterisation skills among UK endoscopists and the impact of a brief training intervention. Frontline Gastroenterology. 2017 Jan;8(1):2-7. DOI: 10.1136/flgastro-2016-100689.

65. Khan T, Cinnor B, Gupta N, Hosford L, Bansal A, Olyaee MS, et al. Didactic training vs. computer-based self-learning in the prediction of diminutive colon polyp histology by trainees: a randomized controlled study. Endoscopy. 2017 Dec;49(12):1243-50. DOI: 10.1055/s-0043-116015.

66. McGill SK, Soetikno R, Rastogi A, Rouse RV, Sato T, Bansal A, et al. Endoscopists can sustain high performance for the optical diagnosis of colorectal polyps following standardized and continued training. Endoscopy. 2015 Mar;47(3):200-6. DOI: 10.1055/s-0034-1378096.

67. Hamet P, Tremblay J. Artificial intelligence in medicine. Metabolism: Clinical and Experimental. 2017 Apr;69s:S36-s40. DOI: 10.1016/j.metabol.2017.01.011.

68. Niazi MKK, Parwani AV, Gurcan MN. Digital pathology and artificial intelligence. The Lancet Oncology. 2019 May;20(5):e253-e61. DOI: 10.1016/s1470-2045(19)30154-8.

69. Wang L, Yang S, Yang S, Zhao C, Tian G, Gao Y, et al. Automatic thyroid nodule recognition and diagnosis in ultrasound imaging with the YOLOv2 neural network. World Journal of Surgical Oncology. 2019 Jan 8;17(1):12. DOI: 10.1186/s12957-019-1558-z.

70. Gutierrez-Martinez J, Pineda C, Sandoval H, Bernal-Gonzalez A. Computer-aided diagnosis in rheumatic diseases using ultrasound: an overview. Clinical Rheumatology. 2019 Nov 6. DOI: 10.1007/s10067-019-04791-z.

71. Alagappan M, Brown JRG, Mori Y, Berzin TM. Artificial intelligence in gastrointestinal endoscopy: The future is almost here. World Journal of Gastrointestinal Endoscopy. 2018 Oct 16;10(10):239-49. DOI: 10.4253/wjge.v10.i10.239.

72. Vennemann B, Obrist D, Rosgen T. Automated diagnosis of heart valve degradation using novelty detection algorithms and machine learning. PLoSOne. 2019;14(9):e0222983. DOI: 10.1371/journal.pone.0222983.

73. Munson MC, Plewman DL, Baumer KM, Henning R, Zahler CT, Kietzman AT, et al. Autonomous early detection of eye disease in childhood photographs. Science Advances. 2019 Oct;5(10):eaax6363. DOI: 10.1126/sciadv.aax6363.

74. Thomsen K, Iversen L, Titlestad TL, Winther O. Systematic review of machine learning for diagnosis and prognosis in dermatology. The Journal of Dermatological Treatment. 2019 Oct 31:1-15. DOI: 10.1080/09546634.2019.1682500.

75. Clarke S, Karoly PJ, Nurse E, Seneviratne U, Taylor J, Knight-Sadler R, et al. Computer-assisted EEG diagnostic review for idiopathic generalized epilepsy. Epilepsy & Behavior : E&B. 2019 Oct 29:106556. DOI: 10.1016/j.yebeh.2019.106556.

76. Mori Y, Kudo SE, Chiu PW, Singh R, Misawa M, Wakamura K, et al. Impact of an automated system for endocytoscopic diagnosis of small colorectal lesions: an international web-based study. Endoscopy. 2016 Aug 5. DOI: 10.1055/s-0042-113609.

77. Misawa M, Kudo SE, Mori Y, Nakamura H, Kataoka S, Maeda Y, et al. Characterization of colorectal lesions using a computer-aided diagnostic system for narrow-band imaging endocytoscopy. Gastroenterology. 2016 Jun;150(7):1531-2.e3. DOI: 10.1053/j.gastro.2016.04.004.

78. Kominami Y, Yoshida S, Tanaka S, Sanomura Y, Hirakawa T, Raytchev B, et al. Computer-aided diagnosis of colorectal polyp histology by using a real-time image recognition system and narrow-band imaging magnifying colonoscopy. Gastrointest Endosc. 2016 Mar;83(3):643-9. DOI: 10.1016/j.gie.2015.08.004.

79. Zachariah R, Samarasena J, Luba D, Duh E, Dao T, Requa J, et al. Prediction of polyp pathology using convolutional neural networks achieves 'resect and discard' thresholds. The American Journal of Gastroenterology. 2019 Oct 23. DOI: 10.14309/ajg.0000000000000429.

80. Rutter MD, Chattree A, Barbour JA, Thomas-Gibson S, Bhandari P, Saunders BP, et al. British Society of Gastroenterology/Association of Coloproctologists of Great Britain and Ireland guidelines for the management of large non-pedunculated colorectal polyps. Gut. 2015 Dec;64(12):1847-73. DOI: 10.1136/gutjnl-2015-309576.

81. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, De Ceglie A, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2015 Sep;47(9):829-54. DOI: 10.1055/s-0034-1392882.

82. Xie HQ, Zhong WZ. Outcomes of colonic endoscopic mucosal resection for large polyps in elderly patients. Journal of Laparoendoscopic & Advanced Surgical Techniques Part A. 2016 Jul 7. DOI: 10.1089/lap.2015.0475.

83. Moss A, Bourke MJ, Williams SJ, Hourigan LF, Brown G, Tam W, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterology. 2011;140(7):1909-18. DOI: 10.1053/j.gastro.2011.02.062.

84. Burgess NG, Bourke MJ. Endoscopic resection of colorectal lesions: The narrowing divide between east and west. Digestive endoscopy. Official Journal of the Japan Gastroenterological Endoscopy Society. 2016 Apr;28(3):296-305. DOI: 10.1111/den.12515.

85. Schachschal G, Mayr M, Treszl A, Balzer K, Wegscheider K, Aschenbeck J, et al. Endoscopic versus histological characterisation of polyps during screening colonoscopy. Gut. 2014 Mar;63(3):458-65. DOI: 10.1136/gutjnl-2013-304562.

86. Tate DJ, Klein A, Desomer L, Brown GJ, Hourigan LF, Moss A, et al. 391 Predicting adenoma recurrence after colonic endoscopic mucosal resection; the Sydney EMR Recurrence Tool (SERT). Gastrointestinal Endoscopy. 2016;83(5):AB142. DOI: 10.1016/j.gie.2016.03.083.

87. Desomer L, Tutticci N, Tate DJ, Williams SJ, McLeod D, Bourke MJ. A standardized imaging protocol is accurate in detecting recurrence after EMR. Gastrointest Endosc. 2016 Jun 22. DOI: 10.1016/j.gie.2016.06.031.

Chapter 2

Sessile serrated adenoma/polyps: Where are we at in 2016?

This chapter offers a brief summary of a paper published in the *World Journal of Gastroenterology*. The statement of authorship and paper (.pdf) 'Sessile serrated adenoma/ polyps: Where are we at in 2016?' follow over the page.

2.1 Summary

As I had started the literature review, the novelty of the serrated pathway and the recognition of the sessile serrated adenoma/polyps (SSA/P) as a pre-malignant lesion became evident. There is a growing amount of evidence on the contribution of such a pathway to CRC. However, at the same time, some clinicians and researchers resist the idea that not all serrated lesions are benign.

In this narrative review, the literature on SSA/Ps is summarised and a brief explanation on the different pathways leading to CRC is provided. In addition, the role of the SSA/Ps is highlighted and details are given on detection, characterisation, malignancy potential and endoscopic treatment for this type of colorectal lesion.

The paper substantiates the necessity of including SSA/P in future research and clinical practice.

2.2 Statement of authorship

Statement of Authorship

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Name of Principal Author 1 (Supervisor)	Rajvinder Singh		
Contribution to the Paper	Participated in the literature review, manuscript preparation and critical revision for important intellectual content. Revised, read and approved the final version of the manuscript.		
Overall percentage (%)	40%		
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Name of Principal Author 2 (Candidate)	Leonardo Zorron Cheng Tao Pu		
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Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Name of Co-Author	Doreen Siew Ching Koay		
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MINIREVIEWS

Sessile serrated adenoma/polyps: Where are we at in 2016?

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Abstract

It is currently known that colorectal cancers (CRC) arise from 3 different pathways: the adenoma to carcinoma chromosomal instability pathway (50%-70%); the mutator "Lynch syndrome" route (3%-5%); and the serrated pathway (30%-35%). The World Health Organization has classified serrated polyps into three types of lesions: hyperplastic polyps (HP), sessile serrated adenomas/polyps (SSA/P) and traditional serrated adenomas (TSA), the latter two strongly associated with development of CRCs. HPs do not cause cancer and TSAs are rare. SSA/P appear to be the responsible precursor lesion for the development of cancers through the serrated pathway. Both HPs and SSA/Ps appear morphologically similar. SSA/P are difficult to detect. The margins are normally inconspicuous. *En bloc* resection of these polyps can hence be troublesome. A careful examination of borders, submucosal injection of a dye solution (for larger lesions) and resection of a rim of normal tissue around the lesion may ensure total eradication of these lesions.

Key words: Colonoscopy; Sessile serrated adenoma/polyp; Serrated lesion; Colorectal polyps; Colorectal cancer; Polypectomy; Image enhancing endoscopy; Narrow band imaging, Endocytoscopy

Core tip: Colorectal cancers (CRC) arise from 3 pathways: adenoma to carcinoma; "Lynch syndrome"; and serrated. There are 3 types of serrated lesions namely: Hyperplastic Polyps, Sessile Serrated Adenomas/Polyps and Traditional Serrated Adenomas, the latter two are associated with CRC. A careful examination of borders, submucosal injection with dye and ensuring that a rim of normal tissue is removed is paramount.

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INTRODUCTION

Colorectal cancer (CRC) is a major health concern, especially in western countries. According to the American Cancer Society's estimates, CRC accounts for almost 50000 deaths in the United States with almost 130000 new cases diagnosed in 2016. It is the third commonest type of cancer. Effective screening programs for identification of malignant and premalignant colorectal lesions are thus of utmost importance. In the last few decades the adenoma to adenocarcinoma pathway has been well recognized. For some time it was believed to be the only pathway apart from the "Lynch syndrome" route that results in the development of CRC. The effort to detect and eradicate adenoma have been the main goal in preventive colorectal programs, leading to improved outcomes. Zauber *et al*[1] showed that colonoscopic removal of adenomatous polyps led to a 53% reduction in mortality from CRC during the first 10 years after polypectomy.

It is currently believed that CRC arises from 3 different pathways: the adenoma to carcinoma pathway which accounts for about 50%-70% of cancers; through the mutator "Lynch syndrome" route (3%-5%); and more recently the serrated pathway (30%-35%). The latter have become increasingly recognized as a separate route which could lead to the development of CRC[2].

This triplet division is based on the combined clinical-molecular characteristics of the lesions. A deeper understanding of the molecular pathways in CRC have been described by Jass in 2007[3] and updated by Phipps *et al*[4] in 2015. They described 5 molecular subtypes and associated genetic distortions to describe each one. Subtypes 1, 2 and 3 are related to the serrated pathway. Subtypes 1 and 2 are either microsatellite instable (MSI)-high or microsatellite stable (MSS)/MSI-low cancers which have the CpG island methylator phenotype (CIMP) and *BRAF*-mutation but are *KRAS* negative. The third subtype represents an alternative pathway which originates in *KRAS* mutation with no CIMP, *BRAF* or MSI association. Subtypes 2 and 3 have a higher association with mortality[4]. Subtype 4 reflects CRC arising from the traditional adenoma-carcinoma sequence, and are MSS/MSI-low, CIMP, *BRAF* and *KRAS* negative. Subtype 5 indicates lynch syndrome and is associated with high prevalence of a family history of CRC. They are MSI-high but CIMP, *BRAF* and *KRAS* negative.

The serrated pathway is much less well understood. Systematic resection of premalignant serrated lesions could further improve the outcomes of CRC screening programs. One of the main problems with this protocol is the difficulty in identifying these lesions. Unlike adenomas, not all serrated lesions are linked to colorectal cancer. According to the World Health Organization, there are three types of serrated lesions: Hyperplastic polyps (HP), sessile serrated adenomas/polyps (SSA/P) and traditional serrated adenomas (TSA). TSA is usually easy to identify due to its protuberant pine cone-shape. While SSA/P is also associated with cancer, HP is not and their discrimination is troublesome as they look morphologically similar at colonoscopy, even with image enhancing endoscopy (IEE) techniques. Despite the adoption of numerous different classifications, the ability to predict HP from SSA/P has unfortunately been overlooked[5,6]. More recently, a newly proposed approach known as Workgroup Serrated polypS and Polyposis WASP classification has allowed the distinction between HP and SSA/P with reasonable accuracy[7]. It consists of cloud-like surface, indistinctive borders, irregular margins and open pit patterns, features described as being associated with SSA/P in another previous study[8]. The need to adequately identify SSA/P from HP arises from evidence supporting SSA/P as the major malignant source amongst serrated lesions[2,9-12].

IEE

Detecting and characterizing colorectal lesions by IEE has been reported in several articles[13-17] and has been found to have 92.7% sensitivity and 87.3% specificity in differentiating adenomas/adenocarcinomas from "non-neoplastic" lesions[18]. Differentiating serrated lesions, specifically SSA/P from HP is more challenging. The incidence of serrated lesions in the overall population is 5%-8% (contrasting with 30%-40% for adenomas), and they are more difficult to see due to their colour and shape[8,19,20]. Their rarity and discreet morphology could be why there is a longer learning curve compared to that for adenomas[21-24].

The evaluation of dysplasia within the SSA/Ps could also be of value. It has been described by Chino *et al*[25] 2016 that the evaluation of crypts and submu-

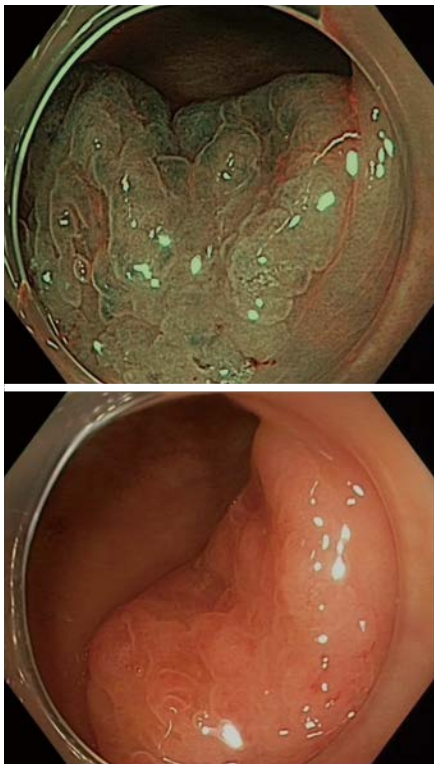

Figure 1 Inconspicuous margins of a sessile serrated adenomas/polyps with and without narrow-band imaging.

cosal vessels with narrow band imaging (NBI) and magnification might be useful in evaluating dysplasia in SSA/P, which leads to poorer outcomes.

Although there is certainly enthusiasm for IEE techniques, histopathology remains the gold standard for evaluating colorectal lesions. Nonetheless, improving technology that could be used by the endoscopist in real time would definitely be beneficial for serrated lesions as it has been for adenomas[26]. This technology will need to provide immediate feedback and accurately predict the final histopathology (Figure 1).

SSA/P AND HP DIFFERENTIATION

A conceptual way to define each serrated lesion is based on differences in the proliferation zones within the serrated crypts in each group[27]. In HP, the expanded proliferation zone is located at the base of the crypts and cells mature towards the surface symmetrically. In SSA/P, the proliferation zone is to the side of the crypts instead of the base, resulting in maturation of epithelial cells laterally, towards the surface and the base, leading to crypt base dilatation (pattern Ⅱ-open). Within SSA/P, the presence of dysplasia is usually evident and must be accompanied by SSA/P component adjacent to it once its histopathology is similar to adenomas. Unfortunately, this theoretical classification may be misleading. Confounded even by expert pathologists, the poor agreement for the diagnosis of villous features or high grade dysplasia has a 10-fold variability[28-30].

New techniques for real-time *in vivo* optical diagnosis using IEE have been developed to potentially predict histology and perhaps permit a more practical and economical approach for low-risk polyps; for example the "resect and discard" approach[31-34]. There is evidence from several original articles and meta-analyses that *in vivo* optical diagnosis using either NBI or Fujinon intelligent chromoendoscopy would be more cost-effective compared to histology without significant changes in follow-up decision, especially for diminutive polyps[34-37]. The American Society for Gastrointestinal Endoscopy statement of 2011 (Preservation and Incorporation of Valuable endoscopic Innovations) describes the standards that new technologies have to achieve in order to be implemented. For the "resect and discard" strategy, it asks for ⩾ 90% agreement in the assignment of post-polypectomy surveillance intervals when compared with decisions based on histopathology. With regards to the policy of leaving suspected rectosigmoid hyperplastic polyps measuring ⩽ 5 mm in place, a ⩾ 90% negative predictive value for adenomatous histology is mandated[31]. Abu Dayyeh *et al*[38] on behalf of the American Societies for Gastrointestinal Endoscopy (ASGE) Technology Committee in 2015 reported in a meta-analysis that the diagnostic value of IEE for diminutive colorectal polyps achieved a pooled NPV 91% and pooled follow-up agreement of 89%. Despite the pooled analysis for agreement in the assignment of surveillance intervals which did not reach the 90% threshold for NBI; experienced endoscopists were able to exceed this (93%) when the diagnosis was made with high confidence.

PREDICTORS OF MALIGNANCY AMONG SSA/P

The most common group of lesions are the diminutive polyps (⩽ 5 mm in size), which represent approximately 60% of all polyps detected at primary screening colonoscopy. Their overall association with advanced pathology is low but not negligible[39,40]. On the contrary, Burgess *et al*[41] have demonstrated that size matters in terms of SSA/P. For every 10 mm increase in lesion size, the OR is 1.90 for cytological dysplasia. SSA/P with cytological dysplasia (SSA/P-D) is also associated with presence of 0-Is component of the Paris' Classification (OR = 3.1), Kudo's pit pattern Ⅲ, Ⅳ or Ⅴ (OR = 3.98) and increasing age (OR = 1.69 per decade).

Yamada *et al*[32] recently described the presence of dilated branch vessels as an aspect of SSA/Ps with dysplasia. Apart from their characteristics at chromoendoscopy and magnification[42,43], there are some aspects that we can use to distinguish SSA/Ps with and without malignancy potential.

Endocytoscopy is an emerging modality with

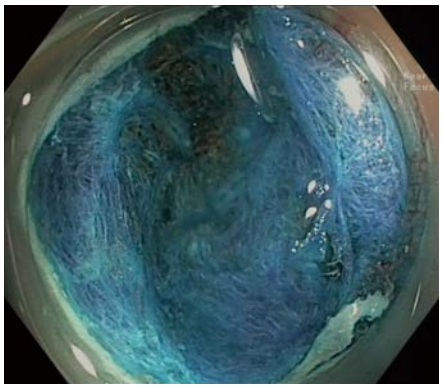

Figure 2 Resection of a sessile serrated adenomas/polyps with dye of submucosal layer with indigo carmine - no residual lesion.

diagnostic potential for SSA/P. It allows *in vivo* visualization of cells and nuclei facilitating precise real-time pathological prediction. Oval gland lumens with small round nuclei has a sensitivity of 83.3% and specificity of 97.8% for the diagnosis of SSA/P. It is also a promising tool for diagnosing SSA/P-D due to its ability to detect morphological changes in the nuclei as described by Mori *et al*[44] and Kutsukawa *et al*[45].

OPTIMAL RESECTION OF AN SSA/P

Numerous studies have grim numbers in regards to SSA/P complete resection rates[46-48]. Against these odds, a more recent study from our group[49] studied the resection of 2000 lateral spreading tumors and attributed the high recurrence to the inconspicuous margins of the SSA/P, which was overcome with IEE techniques. Submucosal instillation of a dye based solution (for larger lesions), a careful examination of borders and a rim of normal tissue resected together with the lesion may have affected the high rate of complete removal of the SSA/P. It is evident the contribution that advanced endoscopy apparel and endoscopist's expertise is essential[50] in order to keep the recurrence of resection as low as 7%, as described by Pellise *et al*[49] (Figure 2).

FOLLOW-UP

The current guidelines from the ASGE and European Societies for Gastrointestinal Endoscopy advocates the standard 5-10 years surveillance period for low risk lesions (SSA/*P* < 10 mm and without dysplasia), in patients without serrated polyposis syndrome. Patients with larger SSA/Ps or with dysplasia should have their colonoscopy repeated in 3 years-time[51,52]. The serrated polyposis syndrome is defined if any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis; if at least five serrated polyps are found proximal to the sigmoid colon (at least 2 with ⩾ 10 mm); and if more than 20 serrated polyps of any size distributed throughout the colon. In these cases, the follow-up should be at 1 year[51]. The major problem is that these guidelines rely upon the assumption that the serrated lesions are detected and resected adequately, which is not always the case.

CONCLUSION

SSA/P is an important pre-malignant lesion that can easily be missed. Efforts must be made in order to alter the nomenclature of "non-neoplastic lesions" to non-adenomatous lesions as the role of serrated lesions in the development of colorectal cancer is now well established. A longer training must be pursued and cutting-edge IEE technologies developed and studied in order to diminish the miss rate for serrated lesions. The implementation of a "serrated polyps detection rate" could be implemented alongside the "adenoma detection rate" as a quality indicator for colonoscopy.

REFERENCES

1 **Zauber AG**, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET, Waye JD. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; **366**: 687-696 [PMID: 22356322 DOI: 10.1056/NEJMoa1100370]

2 **Erichsen R**, Baron JA, Hamilton-Dutoit SJ, Snover DC, Torlakovic EE, Pedersen L, Frøslev T, Vyberg M, Hamilton SR, Sørensen HT. Increased Risk of Colorectal Cancer Development Among Patients With Serrated Polyps. *Gastroenterology* 2016; **150**: 895-902.e5 [PMID: 26677986 DOI: 10.1053/j.gastro.2015.11.046]

3 **Jass JR**. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology* 2007; **50**: 113-130 [PMID: 17204026]

4 **Phipps AI**, Limburg PJ, Baron JA, Burnett-Hartman AN, Weisenberger DJ, Laird PW, Sinicrope FA, Rosty C, Buchanan DD, Potter JD, Newcomb PA. Association between molecular subtypes of colorectal cancer and patient survival. *Gastroenterology* 2015; **148**: 77-87.e2 [PMID: 25280443 DOI: 10.1053/j.gastro.2014.09.038]

5 **Hewett DG**, Kaltenbach T, Sano Y, Tanaka S, Saunders BP, Ponchon T, Soetikno R, Rex DK. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. *Gastroenterology* 2012; **143**: 599-607.e1 [PMID: 22609383 DOI: 10.1053/j.gastro.2012.05.006]

6 **Kumar S**, Fioritto A, Mitani A, Desai M, Gunaratnam N, Ladabaum U. Optical biopsy of sessile serrated adenomas: do these lesions resemble hyperplastic polyps under narrow-band imaging? *Gastrointest Endosc* 2013; **78**: 902-909 [PMID: 23849819]

7 **IJspeert JE**, Bastiaansen BA, van Leerdam ME, Meijer GA, van Eeden S, Sanduleanu S, Schoon EJ, Bisseling TM, Spaander MC, van Lelyveld N, Bargeman M, Wang J, Dekker E. Development and validation of the WASP classification system for optical diagnosis of adenomas, hyperplastic polyps and sessile serrated adenomas/polyps. *Gut* 2016; **65**: 963-970 [PMID: 25753029 DOI: 10.1136/gutjnl-2014-308411]

8 **Hazewinkel Y**, López-Cerón M, East JE, Rastogi A, Pellisé M, Nakajima T, van Eeden S, Tytgat KM, Fockens P, Dekker E. Endoscopic features of sessile serrated adenomas: validation by international experts using high-resolution white-light endoscopy and narrow-band imaging. *Gastrointest Endosc* 2013; **77**: 916-924 [PMID: 23433877 DOI: 10.1016/j.gie.2012.12.018]

9 **Huang CS**, O'brien MJ, Yang S, Farraye FA. Hyperplastic polyps,

serrated adenomas, and the serrated polyp neoplasia pathway. *Am J Gastroenterol* 2004; **99**: 2242-2255 [PMID: 15555008]
10 **Kawasaki K**, Kurahara K, Yanai S, Oshiro Y, Yao T, Kobayashi H, Nakamura S, Fuchigami T, Sugai T, Matsumoto T. Colonoscopic features and malignant potential of sessile serrated adenomas: comparison with other serrated lesions and conventional adenomas. *Colorectal Dis* 2016; **18**: 795-802 [PMID: 26784017 DOI: 10.1111/codi.13276]
11 **Chino A**, Yamamoto N, Kato Y, Morishige K, Ishikawa H, Kishihara T, Fujisaki J, Ishikawa Y, Tamegai Y, Igarashi M. The frequency of early colorectal cancer derived from sessile serrated adenoma/polyps among 1858 serrated polyps from a single institution. *Int J Colorectal Dis* 2016; **31**: 343-349 [PMID: 26510850 DOI: 10.1007/s00384-015-2416-2]
12 **Teriaky A**, Driman DK, Chande N. Outcomes of a 5-year follow-up of patients with sessile serrated adenomas. *Scand J Gastroenterol* 2012; **47**: 178-183 [PMID: 22229626 DOI: 10.3109/00365521.2011.645499]
13 **Kanao H**, Tanaka S, Oka S, Hirata M, Yoshida S, Chayama K. Narrow-band imaging magnification predicts the histology and invasion depth of colorectal tumors. *Gastrointest Endosc* 2009; **69**: 631-636 [PMID: 19251003 DOI: 10.1016/j.gie.2008.08.028]
14 **Tanaka S**, Sano Y. Aim to unify the narrow band imaging (NBI) magnifying classification for colorectal tumors: current status in Japan from a summary of the consensus symposium in the 79th Annual Meeting of the Japan Gastroenterological Endoscopy Society. *Dig Endosc* 2011; **23** Suppl 1: 131-139 [PMID: 21535219 DOI: 10.1111/j.1443-1661.2011.01106.x]
15 **Inoue H**, Yokoyama A, Kudo SE. [Ultrahigh magnifying endoscopy: development of CM double staining for endocytoscopy and its safety]. *Nihon Rinsho* 2010; **68**: 1247-1252 [PMID: 20662202]
16 **Singh R**, Chen Yi Mei SL, Tam W, Raju D, Ruszkiewicz A. Real-time histology with the endocytoscope. *World J Gastroenterol* 2010; **16**: 5016-5019 [PMID: 20976836]
17 **Kudo S**, Hirota S, Nakajima T, Hosobe S, Kusaka H, Kobayashi T, Himori M, Yagyuu A. Colorectal tumours and pit pattern. *J Clin Pathol* 1994; **47**: 880-885 [PMID: 7962600]
18 **Li M**, Ali SM, Umm-a-OmarahGilani S, Liu J, Li YQ, Zuo XL. Kudo's pit pattern classification for colorectal neoplasms: a meta-analysis. *World J Gastroenterol* 2014; **20**: 12649-12656 [PMID: 25253970 DOI: 10.3748/wjg.v20.i35.12649]
19 **Abdeljawad K**, Vemulapalli KC, Kahi CJ, Cummings OW, Snover DC, Rex DK. Sessile serrated polyp prevalence determined by a colonoscopist with a high lesion detection rate and an experienced pathologist. *Gastrointest Endosc* 2015; **81**: 517-524 [PMID: 24998465 DOI: 10.1016/j.gie.2014.04.064]
20 **Sano W**, Sano Y, Iwatate M, Hasuike N, Hattori S, Kosaka H, Ikumoto T, Kotaka M, Fujimori T. Prospective evaluation of the proportion of sessile serrated adenoma/polyps in endoscopically diagnosed colorectal polyps with hyperplastic features. *Endosc Int Open* 2015; **3**: E354-E358 [PMID: 26357681 DOI: 10.1055/s-0034-1391948]
21 **Ignjatovic A**, Thomas-Gibson S, East JE, Haycock A, Bassett P, Bhandari P, Man R, Suzuki N, Saunders BP. Development and validation of a training module on the use of narrow-band imaging in differentiation of small adenomas from hyperplastic colorectal polyps. *Gastrointest Endosc* 2011; **73**: 128-133 [PMID: 21184878 DOI: 10.1016/j.gie.2010.09.021]
22 **Raghavendra M**, Hewett DG, Rex DK. Differentiating adenomas from hyperplastic colorectal polyps: narrow-band imaging can be learned in 20 minutes. *Gastrointest Endosc* 2010; **72**: 572-576 [PMID: 20561618 DOI: 10.1016/j.gie.2010.03.1124]
23 **Rastogi A**, Rao DS, Gupta N, Grisolano SW, Buckles DC, Sidorenko E, Bonino J, Matsuda T, Dekker E, Kaltenbach T, Singh R, Wani S, Sharma P, Olyaee MS, Bansal A, East JE. Impact of a computer-based teaching module on characterization of diminutive colon polyps by using narrow-band imaging by non-experts in academic and community practice: a video-based study. *Gastrointest Endosc* 2014; **79**: 390-398 [PMID: 24021492]
24 **Higashi R**, Uraoka T, Kato J, Kuwaki K, Ishikawa S, Saito Y, Matsuda T, Ikematsu H, Sano Y, Suzuki S, Murakami Y, Yamamoto K. Diagnostic accuracy of narrow-band imaging and pit pattern analysis significantly improved for less-experienced endoscopists after an expanded training program. *Gastrointest Endosc* 2010; **72**: 127-135 [PMID: 20493482 DOI: 10.1016/j.gie.2010.01.054]
25 **Chino A**, Osumi H, Kishihara T, Morishige K, Ishikawa H, Tamegai Y, Igarashi M. Advantages of magnifying narrow-band imaging for diagnosing colorectal cancer coexisting with sessile serrated adenoma/polyp. *Dig Endosc* 2016; **28** Suppl 1: 53-59 [PMID: 26864801 DOI: 10.1111/den.12631]
26 **Dacosta RS**, Wilson BC, Marcon NE. New optical technologies for earlier endoscopic diagnosis of premalignant gastrointestinal lesions. *J Gastroenterol Hepatol* 2002; **17** Suppl: S85-S104 [PMID: 12000596]
27 **Torlakovic EE**, Gomez JD, Driman DK, Parfitt JR, Wang C, Benerjee T, Snover DC. Sessile serrated adenoma (SSA) vs. traditional serrated adenoma (TSA). *Am J Surg Pathol* 2008; **32**: 21-29 [PMID: 18162766 DOI: 10.1097/PAS.0b013e318157f002]
28 **Terry MB**, Neugut AI, Bostick RM, Potter JD, Haile RW, Fenoglio-Preiser CM. Reliability in the classification of advanced colorectal adenomas. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 660-663 [PMID: 12101114]
29 **Costantini M**, Sciallero S, Giannini A, Gatteschi B, Rinaldi P, Lanzanova G, Bonelli L, Casetti T, Bertinelli E, Giuliani O, Castiglione G, Mantellini P, Naldoni C, Bruzzi P. Interobserver agreement in the histologic diagnosis of colorectal polyps. the experience of the multicenter adenoma colorectal study (SMAC). *J Clin Epidemiol* 2003; **56**: 209-214 [PMID: 12725874]
30 **Lasisi F**, Mouchli A, Riddell R, Goldblum JR, Cummings OW, Ulbright TM, Rex DK. Agreement in interpreting villous elements and dysplasia in adenomas less than one centimetre in size. *Dig Liver Dis* 2013; **45**: 1049-1055 [PMID: 23871251 DOI: 10.1016/j.dld.2013.05.014]
31 **Rex DK**, Kahi C, O'Brien M, Levin TR, Pohl H, Rastogi A, Burgart L, Imperiale T, Ladabaum U, Cohen J, Lieberman DA. The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on real-time endoscopic assessment of the histology of diminutive colorectal polyps. *Gastrointest Endosc* 2011; **73**: 419-422 [PMID: 21353837 DOI: 10.1016/j.gie.2011.01.023]
32 **Yamada M**, Sakamoto T, Otake Y, Nakajima T, Kuchiba A, Taniguchi H, Sekine S, Kushima R, Ramberan H, Parra-Blanco A, Fujii T, Matsuda T, Saito Y. Investigating endoscopic features of sessile serrated adenomas/polyps by using narrow-band imaging with optical magnification. *Gastrointest Endosc* 2015; **82**: 108-117 [PMID: 25840928 DOI: 10.1016/j.gie.2014.12.037]
33 **Iwatate M**, Sano Y, Hattori S, Sano W, Hasuike N, Ikumoto T, Kotaka M, Murakami Y, Hewett DG, Soetikno R, Kaltenbach T, Fujimori T. The addition of high magnifying endoscopy improves rates of high confidence optical diagnosis of colorectal polyps. *Endosc Int Open* 2015; **3**: E140-E145 [PMID: 26135657 DOI: 10.1055/s-0034-1391362]
34 **Ignjatovic A**, East JE, Suzuki N, Vance M, Guenther T, Saunders BP. Optical diagnosis of small colorectal polyps at routine colonoscopy (Detect InSpect ChAracterise Resect and Discard; DISCARD trial): a prospective cohort study. *Lancet Oncol* 2009; **10**: 1171-1178 [PMID: 19910250 DOI: 10.1016/S1470-2045(09)70329-8]
35 **Gupta N**, Bansal A, Rao D, Early DS, Jonnalagadda S, Edmundowicz SA, Sharma P, Rastogi A. Accuracy of in vivo optical diagnosis of colon polyp histology by narrow-band imaging in predicting colonoscopy surveillance intervals. *Gastrointest Endosc* 2012; **75**: 494-502 [PMID: 22032847 DOI: 10.1016/j.gie.2011.08.002]
36 **Longcroft-Wheaton GR**, Higgins B, Bhandari P. Flexible spectral imaging color enhancement and indigo carmine in neoplasia diagnosis during colonoscopy: a large prospective UK series. *Eur J Gastroenterol Hepatol* 2011; **23**: 903-911 [PMID: 21795980 DOI: 10.1097/MEG.0b013e328349e27]

37 **Hassan C**, Pickhardt PJ, Rex DK. A resect and discard strategy would improve cost-effectiveness of colorectal cancer screening. *Clin Gastroenterol Hepatol* 2010; **8**: 865-869, 869.e1-3 [PMID: 20621680 DOI: 10.1016/j.cgh.2010.05.018]

38 **Abu Dayyeh BK**, Thosani N, Konda V, Wallace MB, Rex DK, Chauhan SS, Hwang JH, Komanduri S, Manfredi M, Maple JT, Murad FM, Siddiqui UD, Banerjee S. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting real-time endoscopic assessment of the histology of diminutive colorectal polyps. *Gastrointest Endosc* 2015; **81**: 502.e1-502.e16 [PMID: 25597420 DOI: 10.1016/j.gie.2014.12.022]

39 **Regula J**, Rupinski M, Kraszewska E, Polkowski M, Pachlewski J, Orlowska J, Nowacki MP, Butruk E. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. *N Engl J Med* 2006; **355**: 1863-1872 [PMID: 17079760]

40 **Gschwantler M**, Kriwanek S, Langner E, Göritzer B, Schrutka-Kölbl C, Brownstone E, Feichtinger H, Weiss W. High-grade dysplasia and invasive carcinoma in colorectal adenomas: a multivariate analysis of the impact of adenoma and patient characteristics. *Eur J Gastroenterol Hepatol* 2002; **14**: 183-188 [PMID: 11981343]

41 **Burgess NG**, Pellise M, Nanda KS, Hourigan LF, Zanati SA, Brown GJ, Singh R, Williams SJ, Raftopoulos SC, Ormonde D, Moss A, Byth K, P'Ng H, McLeod D, Bourke MJ. Clinical and endoscopic predictors of cytological dysplasia or cancer in a prospective multicentre study of large sessile serrated adenomas/polyps. *Gut* 2016; **65**: 437-446 [PMID: 25731869 DOI: 10.1136/gutjnl-2014-308603]

42 **Ignjatovic A**, East JE, Guenther T, Hoare J, Morris J, Ragunath K, Shonde A, Simmons J, Suzuki N, Thomas-Gibson S, Saunders BP. What is the most reliable imaging modality for small colonic polyp characterization? Study of white-light, autofluorescence, and narrow-band imaging. *Endoscopy* 2011; **43**: 94-99 [PMID: 21271465 DOI: 10.1055/s-0030-1256074]

43 **Rex DK**, Clodfelter R, Rahmani F, Fatima H, James-Stevenson TN, Tang JC, Kim HN, McHenry L, Kahi CJ, Rogers NA, Helper DJ, Sagi SV, Kessler WR, Wo JM, Fischer M, Kwo PY. Narrow-band imaging versus white light for the detection of proximal colon serrated lesions: a randomized, controlled trial. *Gastrointest Endosc* 2016; **83**: 166-171 [PMID: 25952085 DOI: 10.1016/j.gie.2015.03.1915]

44 **Mori Y**, Kudo SE, Ogawa Y, Wakamura K, Kudo T, Misawa M, Hayashi T, Katagiri A, Miyachi H, Inoue H, Oka S, Matsuda T. Diagnosis of sessile serrated adenomas/polyps using endocytoscopy (with videos). *Dig Endosc* 2016; **28** Suppl 1: 43-48 [PMID: 26748690 DOI: 10.1111/den.12601]

45 **Kutsukawa M**, Kudo SE, Ikehara N, Ogawa Y, Wakamura K, Mori Y, Ichimasa K, Misawa M, Kudo T, Wada Y, Hayashi T, Miyachi H, Inoue H, Hamatani S. Efficiency of endocytoscopy in differentiating types of serrated polyps. *Gastrointest Endosc* 2014; **79**: 648-656 [PMID: 24119508 DOI: 10.1016/j.gie.2013.08.029]

46 **Khashab M**, Eid E, Rusche M, Rex DK. Incidence and predictors of "late" recurrences after endoscopic piecemeal resection of large sessile adenomas. *Gastrointest Endosc* 2009; **70**: 344-349 [PMID: 19249767 DOI: 10.1016/j.gie.2008.10.037]

47 **Kahi CJ**, Hewett DG, Norton DL, Eckert GJ, Rex DK. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. *Clin Gastroenterol Hepatol* 2011; **9**: 42-46 [PMID: 20888435 DOI: 10.1016/j.cgh.2010.09.013]

48 **Pohl H**, Srivastava A, Bensen SP, Anderson P, Rothstein RI, Gordon SR, Levy LC, Toor A, Mackenzie TA, Rosch T, Robertson DJ. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. *Gastroenterology* 2013; **144**: 74-80.e1 [PMID: 23022496 DOI: 10.1053/j.gastro.2012.09.043]

49 **Pellise M**, Burgess NG, Tutticci N, Hourigan LF, Zanati SA, Brown GJ, Singh R, Williams SJ, Raftopoulos SC, Ormonde D, Moss A, Byth K, P'Ng H, Mahajan H, McLeod D, Bourke MJ. Endoscopic mucosal resection for large serrated lesions in comparison with adenomas: a prospective multicentre study of 2000 lesions. *Gut* 2016; Epub ahead of print [PMID: 26786685 DOI: 10.1136/gutjnl-2015-310249]

50 **Valori R**, Rey JF, Atkin WS, Bretthauer M, Senore C, Hoff G, Kuipers EJ, Altenhofen L, Lambert R, Minoli G. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Quality assurance in endoscopy in colorectal cancer screening and diagnosis. *Endoscopy* 2012; **44** Suppl 3: SE88-SE105 [PMID: 23012124]

51 **Lieberman DA**, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2012; **143**: 844-857 [PMID: 22763141 DOI: 10.1053/j.gastro.2012.06.001]

52 **Hassan C**, Quintero E, Dumonceau JM, Regula J, Brandão C, Chaussade S, Dekker E, Dinis-Ribeiro M, Ferlitsch M, Gimeno-García A, Hazewinkel Y, Jover R, Kalager M, Loberg M, Pox C, Rembacken B, Lieberman D. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2013; **45**: 842-851 [PMID: 24030244 DOI: 10.1055/s-0033-1344548]

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Chapter 3

Different factors are associated with conventional adenoma and serrated colorectal neoplasia

This chapter offers a brief summary of a paper published in the *Nagoya Journal of Medical Science.* The statement of authorship and a copy of the paper 'Different factors are associated with conventional adenoma and serrated colorectal neoplasia' follow over the page.

3.1 Summary

Studies often search for associations of diet and lifestyle with cancer. Colorectal cancer, for instance, has been associated with several dietary factors, including the 'westernized diet' (high fat and red meat, and low fibre intake), a sedentary lifestyle and smoking. As both lifestyle and diet vary greatly between countries, validation studies in different settings are important. In this study, we have looked at different lifestyle factors and diet patterns using a simplified questionnaire. Our goal was to elucidate the association of these lifestyle factors with colorectal lesions in patients coming for elective colonoscopies in a tertiary South Australian hospital. Although similar studies have been performed around the globe on this subject, data from Australia is limited.

All patients undergoing colonoscopy at the Lyell McEwin endoscopy unit were invited to fill a one-page questionnaire regarding their diet and habits (e.g. physical activity, smoking, red meat consumption). 291 procedures were included and assessed for the presence of colorectal lesions. Through multivariable model analysis, it was found that different factors were associated with different lesions. Older age, male gender and smoking were found to be associated with conventional adenomas, whereas diabetes mellitus and family history of CRC were associated with neoplastic serrated polyps.

The association of the above-mentioned factors with colorectal neoplasia concurs with the literature, which is vast when looking at overall lesions. However, the identification of different factors associated with different polyp histological types is a newer approach for which there have been only a limited number of studies. These studies indicate that this is an important subject to explore, as results imply that different mechanisms might be related to the development of each type of lesion.

3.2 Statement of authorship

Statement of Authorship

Title of Paper	Different factors are associated with conventional adenoma and serrated colorectal neoplasia
Publication Status	☑ Published ☑ ~~Accepted for Publication~~ ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
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Name of Principal Author (Candidate)	Leonardo Zorron Cheng Tao Pu		
Contribution to the Paper	Conceptualised and designed the study. Involved in data collection, processing and statistical analysis. Interpreted the results and prepared the manuscript.		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	17/10/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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ORIGINAL PAPER

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Different factors are associated with conventional adenoma and serrated colorectal neoplasia

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ABSTRACT

Current data shows there are differences in factors associated with colorectal neoplasia based on geographical location and cultural settings. There are no studies focusing on the association between environmental factors and colorectal polyps in Australia. The aim of this study was to prospectively evaluate the association of various factors with different colorectal neoplasia histology. We utilized a simplified one-page questionnaire for patients undergoing colonoscopy for information on age; gender; comorbidities; family history of colorectal cancer; physical activity; smoking; diet; alcohol intake; and body mass index. Factors were then evaluated for association with the presence of: (1) neoplastic lesions; (2) conventional adenomas; (3) neoplastic serrated polyps; (4) any lesions (past and present); and (5) hyperplastic polyps. 291 procedures and 260 patients were included. Factors with a p-value <0.2 in a univariate regression were included in an initial multivariable regression model. Backwards elimination was then performed, removing one predictor at a time until only significant predictors remained. In the final multivariable model, age≥65, male gender, type-2 diabetes mellitus, active smoking and family history of colorectal cancer were found to be statistically significant predictors for the presence of colorectal neoplasia. However, the significant predictors found for conventional adenomas (older age, male gender and smoking) were different from the significant predictors for neoplastic serrated polyps (type-2 diabetes mellitus and family history of colorectal cancer). Older age, male gender, type-2 diabetes mellitus, and smoking were significantly associated with the presence of colorectal neoplasia. The factors associated with conventional adenomas differed from those associated with neoplastic serrated polyps.

Keywords: colonoscopy, comorbidity, risk factors, colonic polyps, colonic neoplasms

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Abbreviations:
CRC: Colorectal cancer
BMI: Body mass index
T2DM: Type-2 diabetes mellitus
BBPS: Boston bowel preparation scale
FHCRC: Family history of colorectal cancer

INTRODUCTION

Several factors have been investigated for their association with colorectal cancer (CRC). Due to inductive logic, these same factors are associated with an increased prevalence of CRC precursor lesions: colorectal polyps. For instance, smoking has been associated with both.[1] Another study highlighted in a broader sense that a healthy lifestyle is associated with a lower risk of CRC.[2] In this study, more than 500,000 people were analyzed regarding the impact of various factors on the incidence of CRC (e.g. body mass index – BMI, physical activity, smoking, and diet). Interestingly, they did not find statistical significance for isolated factors but rather identified an overall contribution of a healthier lifestyle towards a lower CRC incidence.

The impact of a healthy lifestyle on colorectal neoplasia can also be found in the East, but with slightly different results. In one retrospective case-control study[3] the evaluation of a healthy lifestyle was based on physical activity (exercises at least three times a week), sufficient sleep (at least 8 hours per day), low red meat consumption (at most three times a week) and a high fiber consumption (at least 300 g per day). In addition, a comorbidity history index was formulated based on previously diagnosed diabetes, hyperlipidemia, inflammatory bowel disease and colorectal polyps. In this study, alcohol intake and smoking did not show any statistical difference in CRC prevalence, contradicting findings in Western literature. Comorbidities such as hyperlipidemia and diabetes have also been correlated with CRC.[3]

In addition to these factors, the Westernized diet has been associated with the development of CRC. Westernized diet is commonly described as a high fat, high red meat and low fiber intake. In a study by Le Marchand,[4] Japanese descendants had an increase in incidence of CRC as soon as the first generation were born overseas (Hawaii). In a more recent case control study, O'Keefe et al[5] studied an intervention to elucidate the extent of the dietary changes on the colonic mucosa. A cross-over of diets between African Americans and a rural population of South Africans has shown reciprocal changes in the colonic mucosa that may be associated with colorectal carcinogenesis.

Even within the same country, there are differences in the results of how and which factors influence colorectal neoplasia. For instance, type-2 diabetes mellitus (T2DM) has been associated with colorectal adenomas in a meta-analysis with high heterogeneity amongst the Asian, American and European studies (I^2 statistics from 45.7% to 52.8%).[6] Six out of the eleven Western studies and four out of six Eastern studies found a positive correlation.

Although research investigating the epidemiology and potential mechanisms of carcinogenesis has been done, data is limited on the uniquely multiethnic and multicultural Australian population. In addition, scarce are the studies that analyze separately the contribution of such factors to individual histological polyp subtypes (i.e. adenomas and serrated polyps). We therefore embarked on a prospective study to evaluate the factors associated with colorectal neoplasia in an Australian cohort.

MATERIALS AND METHODS

Consecutive patients undergoing colonoscopy from August 2016 to January 2018 were invited to participate in the study. The colonoscopes used for the procedures were the Olympus® 190 series and performed by a single proceduralist (RS). This study has been approved by the Central Adelaide Local Health Network human research ethics committee as a low and negligible risk research through the approval number 2008128.

Patients under 18 years old and those unwilling to participate in the study were excluded. In addition, patients with total colectomy, a previous diagnosis or any endoscopic activity of inflammatory bowel disease, familial adenomatous polyposis or Peutz-Jeghers syndrome were excluded. Patients submitted to emergency colonoscopies (e.g. acute bleeding requiring endoscopic hemostasis) were also excluded since the focus of the colonoscopy would most likely not allow for the evaluation and resection of polyps. Only complete colonoscopies were included (i.e. acute angles that did not allow to progress to the caecum/ileo-colic anastomosis were excluded).

During the procedure, the quality of the bowel preparation was evaluated through the Boston bowel preparation scale (BBPS). Patients with BBPS < 6 were excluded. In patients with partial colectomy, a value for BBPS was attributed to the resected segment for comparison purposes. The attributed BBPS corresponded to the mean of the existing colonic segments (minus 0.5 when the result was a decimal).

Prior to the colonoscopy, patients were invited to participate in the research and all questions were clarified. All patients had previously received an explanatory sheet about the study, which was sent along with the bowel preparation kit. On the day of the colonoscopy, a one-page questionnaire was used to collect information on age, gender, family history of CRC (FHCRC), comorbidities and various associated factors prior to the procedure. The information was then correlated with the findings of the colonoscopy.

Habits and dietary factors were used as categorical variables (dichotomy – YES or NO). Physical activity was considered adequate if the patient exercised more than 30 minutes for 3 times a week. Red meat consumption was considered high if patients had eaten more than three times a week. Fiber consumption was conceived to be sensitive and was considered high if they had eaten more than two portions of cereals, fruits, oatmeal, legumes or vegetables per day (roughly equivalent to 30g of fiber per day). Smoking was considered positive if the patient was an active smoker regardless of the amount. Alcohol intake was considered high if greater than two standard drinks for men and one for women were consumed daily. Age and weight (through BMI) were retrieved as continuous variables but dichotomized for analysis purposes (≥65 years of age and 30 kg/m^2, respectively). A FHCRC was defined by the presence of any first or second-degree relatives with CRC.

Habit questions were based on previous studies and chosen in order to simplify the patients' responses. Physical activity, alcohol intake, smoking status and red meat consumption questions were based on the previous study of Hang et al[3] and the Australian National Health and Medical Research Council recommendations.[7]

The responses to the questionnaire were manually computed into an Excel database. The findings of the colonoscopy were entered alongside these. The histology results of the resected specimens were compiled into the database at a later date, once available.

The primary outcome was association of various factors with neoplastic lesions found at the present colonoscopy. Secondary outcomes were the association of various factors with presence of: conventional adenomas; neoplastic serrated polyps; any polyps (past or present); or hyperplastic polyps. The presence of any lesions (past and present) was considered when patients either had any lesions detected in prior procedures (i.e. colonoscopy for surveillance or referred for advanced

endoscopic resection); or in the current procedure for screening or symptoms.

Neoplastic lesions were defined as any conventional adenoma, sessile serrated adenoma/polyp, traditional serrated adenoma or colorectal cancer detected during the colonoscopy. Conventional adenomas were considered present when at least one adenoma (i.e. tubular adenoma, tubulovillous adenoma or villous adenoma) was detected. Neoplastic serrated polyps were considered present when any sessile serrated adenoma/polyp or traditional serrated adenoma were detected during the procedure. All colorectal neoplasia types included were confirmed by histopathology.

For the assessment of association between various factors and proposed outcomes, logistic generalized estimating equation models have been used to account for clustering on patients. Univariate analyses were performed for all factors. Those predictors with a p-value <0.2 in the univariate regression were included in an initial multivariable regression model, one model for each outcome. Backwards elimination was then performed, removing the covariate with highest p-value one at a time until only significant predictors remained at the 0.05 level of significance. The statistical software used was SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Difference of proportions was assessed with the Chi-squared test.

RESULTS

A total of 325 colonoscopies were assessed against the eligibility criteria. From those, 291 were included in the final analysis. Excluded cases consisted mainly of inflammatory bowel disease cases. During the period of the study, 26 patients had their colonoscopies repeated once and 3 had their colonoscopies repeated twice as per the number and/or complexity of the lesions found. These have been accounted for in the statistical model. The mean age of participants was 63.9 and 56% of our cohort was 65 years or older. The average BMI was 28.5 (28.3 for males and 29 for females). Cohort demographics are summarized in [Table 1] and polyp characteristics are summarized in [Table 2]. Conventional adenomas and neoplastic serrated polyps were found concurrently in only 28 (9.6%) procedures. In relation to differences in associated factors between

Table 1 Cohort demographics – n (%)

Total number of procedures	291 (100)
Male gender	156 (53.6)
Indication for the procedure[a]	
Screening	73 (25.3)
Surveillance	146 (50.5)
Symptoms	70 (24.2)
Diabetes mellitus	58 (20.1)
Prophylactic aspirin	49 (17)
Hyperlipidaemia	117 (40.6)
Active smoking	68 (23.7)
High alcohol intake	42 (14.7)
Fibre intake > 30g/day	224 (78.9)
High red meat intake	137 (48.2)
Physical activity adequate	181 (64.2)
Body mass index ≥ 30	97 (33.1)
Family history of colorectal cancer positive	55 (21.1)

[a] For patients referred for endoscopic resection the indication represents the index procedure.

genders, the only factor that was shown to be statistically different was alcohol intake, which was lower in the female cohort [Table 3].

In the initial univariate analysis for neoplastic lesions, patients with ≥65 years old had 2.3 times greater odds of having a past or present polyp compared with patients with <65 years of age. Similarly, patients with T2DM had 2.4 times greater odds of having neoplastic lesions than patients without T2DM.

Being a current smoker, being ≥65 years of age and the use of prophylactic aspirin were all factors found to be associated with conventional adenomas in univariate analyses. The odds were 1.8, 2.3 and 2.4 times greater, respectively. For neoplastic serrated polyps, ≥ 65 years of age, BMI ≥30, T2DM and a FHCRC were factors found to have increased odds of having neoplastic serrated polyps. A statistically significant association was found between the presence of past or present polyps and age (p-value = 0.0006). Those patients who were aged 65 years or older

Table 2 Colorectal lesion occurrence and histology

Colonoscopies n (%)	**Total**	**291 (100)**
	Neoplastic lesion present	196 (67.4)
	Conventional adenoma present	168 (57.7)
	Neoplastic serrated polyp present	45 (15.5)
	Any lesion present (current procedure)	223 (76.6)
	Any lesion present (current or past procedure)	252 (86.6)
Histology n (%)	**Total**	**483 (100)**
	Hyperplastic	56 (11.6)
	Adenoma LGD	298 (61.7)
	Adenoma HGD	22 (4.6)
	SSA/P without dysplasia	75 (15.5)
	SSA/P with dysplasia	10 (2.1)
	Superficial cancer	6 (1.2)
	Invasive cancer	11 (2.3)
	Traditional serrated adenoma	1 (0.2)
	Other	4 (0.8)

LGD: low grade dysplasia, HGD: high grade dysplasia, SSA/P: sessile serrated adenoma/polyp.

Table 3 Prevalence of associated factors in enrolled participants, by gender

	Male – n (%)	**Female – n (%)**
Diabetes mellitus	29 (18.8)	29 (21.6)
Prophylactic aspirin	25 (16.2)	24 (17.9)
Hyperlipidemia	65 (42.2)	52 (38.8)
Active smoking	40 (26.1)	28 (20.9)
High alcohol intake*	33 (21.7)	9 (6.7)
Fiber intake > 30g/day	118 (77.6)	106 (80.3)
High red meat intake	80 (52.6)	57 (43.2)
Physical activity adequate	103 (68.2)	78 (59.5)
Body mass index ≥ 30	47 (30.7)	50 (37.3)
Family history of colorectal cancer positive	23 (16.5)	32 (26.2)

*p<0.01

Table 4 Univariate logistic generalized estimating equation model analysis of association of various factors with colorectal neoplasia

Model#	*Outcome*	*Predictor*	*Comparison value*	*OR (95% CI)*	*p-value*
1	Neoplastic lesions	Age	≥ 65 years	2.27 (1.38 to 3.76)	<0.01
	Neoplastic lesions	T2DM	Currently on medication	2.36 (1.22 to 4.56)	<0.05
2	Conventional adenomas	Age	≥ 65 years	2.33 (1.42 to 3.80)	<0.01
	Conventional adenomas	Prophylactic aspirin	Currently on medication	2.43 (1.10 to 5.36)	<0.05
	Conventional adenomas	Smoking	Active smoking	1.84 (1.01 to 3.35)	<0.05
3	Neoplastic serrated polyps	Age	≥ 65 years	2.04 (1.02 to 4.10)	<0.05
	Neoplastic serrated polyps	T2DM	Currently on medication	3.12 (1.53 to 6.34)	<0.01
	Neoplastic serrated polyps	BMI	≥ 30	2.24 (1.16 to 4.34)	<0.05
	Neoplastic serrated polyps	FHCRC	1st or 2nd degree relative	2.17 (1.07 to 4.42)	<0.05
4	Any lesions (past and present)	Age	≥ 65 years	3.73 (1.75 to 7.94)	<0.01
	Any lesions (past and present)	T2DM	Currently on medication	10.98 (1.46 to 82.41)	<0.05
	Any lesions (past and present)	Hyperlipidemia	Currently on medication	2.43 (1.09 to 5.39)	<0.05
5	Hyperplastic polyps	Gender	Male	5.04 (1.10 to 23.20)	<0.05

T2DM: type 2 diabetes mellitus, BMI: body mass index, FHCRC: family history of colorectal cancer.

had odds of having a past or present polyp 3.7 times greater than patients aged less than 65 years. There was also a statistically significant association found between the presence of past or present polyps and both T2DM and hyperlipidemia. Patients who had T2DM or hyperlipidemia had odds of having a past or present polyp 11.0 and 2.4 times greater, respectively [Table 4].

In the multivariable logistic generalized estimating equation model analysis, a statistically significant association was found between the presence of neoplastic lesions and age, T2DM, gender and smoking, with each predictor controlling for each other and with adjustment for clustering on patient [Table 5]. Those patients who were ≥ 65 years old had odds of having a neoplastic lesion 2.5 times higher, patients with T2DM had odds 2.4 times higher, males had odds 1.7 times higher and current smokers had odds 2.2 times higher.

There was also a statically significant association found between the presence of past or present polyps, age and T2DM. Those patients who were aged 65 or older had 3.4 times greater odds of having a past or present polyp and patients with T2DM had odds 9.7 times higher. The associations between adenomas and age, gender and smoking were also statistically significant. Those patients who were aged 65 or older had odds of having adenomas 2.7 times higher, males had odds 1.7 times higher and current smokers had odds 2.2 times higher. Neoplastic serrated polyps' prevalence was shown to be significantly associated with T2DM and FHCRC. If these factors were present, the odds of having a neoplastic serrated polyp were 3.5 and 2.1 times greater, respectively.

Table 5 Multivariable logistic generalized estimating equation model analysis of association of various factors with colorectal neoplasia

Model#	*Outcome*	*Predictor*	*Comparison value*	*OR (95% CI)*	*p-value*
1	Neoplastic lesions	Age	≥ 65 years	2.51 (1.47 to 4.28)	<0.01
	Neoplastic lesions	T2DM	Currently on medication	2.39 (1.24 to 4.61)	<0.01
	Neoplastic lesions	Gender	Male	1.74 (1.03 to 2.94)	<0.05
	Neoplastic lesions	Smoking	Active smoking	2.19 (1.14 to 4.23)	<0.05
2	Conventional adenomas	Age	≥ 65 years	2.72 (1.62 to 4.58)	<0.01
	Conventional adenomas	Gender	Male	1.70 (1.03 to 2.81)	<0.05
	Conventional adenomas	Smoking	Active smoking	2.24 (1.17 to 4.27)	<0.05
3	Neoplastic serrated polyps	T2DM	Currently on medication	3.52 (1.68 to 7.35)	<0.01
	Neoplastic serrated polyps	Family history of CRC	1st or 2nd degree relative	2.11 (1.01 to 4.40)	<0.05
4	Any lesions (past and present)	Age	≥ 65 years	3.36 (1.56 to 7.24)	<0.01
	Any lesions (past and present)	T2DM	Currently on medication	9.66 (1.29 to 72.45)	<0.05
5	Hyperplastic polyps	Gender	Male	5.04 (1.10 to 23.20)	<0.05

T2DM: type 2 diabetes mellitus, CRC: colorectal cancer.

A subanalysis was also performed looking at factors associated with hyperplastic polyps. For both univariate and multivariate analyses, the only relevant factor associated with the presence of hyperplastic polyps was male gender [Tables 4 and 5].

DISCUSSION

This study revealed that, in a multivariable model, active smokers were 2.2 (95% CI: 1.1, 4.2) times more likely to have colorectal neoplasia than non-smokers. Several other studies have also shown smoking to be associated with colorectal neoplasia, but mainly CRC.[8-11] Regarding polyps, the carcinogens in tobacco are believed to increase the formation and growth rate of conventional adenomas, contributing to an estimated 12% of CRC deaths.[12] In this study, although smoking was associated with conventional adenomas, it was not associated with neoplastic serrated polyps. Hence, tobacco appears to predominantly affect the adenoma-carcinoma pathway. Our results are in contrast to another study,[13] which found that in addition to adenomas (RR 1.29, 95% CI: 1.11, 1.49), smoking was also associated with serrated polyps (RR 2.27, 95% CI: 1.68, 3.06). However, Figueiredo et al[13] considered all serrated polyps for their outcome, whether neoplastic or not. In addition, their increase of serrated polyps was only found when looking at left colon serrated polyps, which are known to rarely be neoplastic.

In a multivariable model, patients with T2DM had 2.4 (95% CI: 1.2, 4.6) times an increased risk of colorectal neoplasia. This concurs with the literature which found that both CRC (RR

1.21, 1.30) and neoplastic polyps (RR 1.52) prevalence are associated with T2DM.[14-16] Interestingly, the association in our study was specifically with serrated neoplastic lesions. This theory is supported by the meta-analysis of Yu et al[16] From all included studies the one that revealed the highest RR was also the only one that included solely sessile serrated adenoma/polyps.

It has been suggested that the hyperinsulinemia and free IGF-1 in insulin resistant T2DM patients may promote the proliferation of colonic epithelial cells, possibly having a tumorigenic effect.[17-19] A study by Yang et al[20] found that T2DM with insulin use ≥1-year was associated with an increased risk of CRC (2.1, 95% CI 1.20, 3.40) as compared to T2DM not managed with insulin. Although a hypothetical mechanism was considered, our results did not show a significant difference in colorectal neoplasia when comparing T2DM patients using insulin as compared to those not using insulin (OR 1.42, 95% CI: 0.36, 5.57). However, this could possibly be due to a type II error.

Our results have some possible public health implications. An estimated 1.7 million Australians suffer from diabetes in addition to the disease being the fastest growing chronic condition in the country, surpassing heart disease and cancer.[21] CRC was the second most commonly diagnosed cancer in Australia in 2018 (behind breast in females and prostate in males), contributing to over 4,000 deaths in one year.[22] As the prevalence of diabetes increases, it may contribute to more cases of CRC and its precursors. Therefore, the addition of associated factors such as T2DM to the current guidelines could potentially allow risk stratification in screening and surveillance colonoscopy protocols.

As expected, men and those older than 65 had a 1.7 (95% CI: 1.03, 2.9) and 2.5 (95% CI: 1.5, 4.3) higher risk of presenting with colorectal neoplasia respectively, in a multivariable model. This is in line with other studies that show a significantly higher incidence of CRC in the 60+ age group[12,23] and in males.[24,25]

There are some limitations to our study. The sample size was limited, and it was based at a single center. In addition, although the assessment of diet through simple questions facilitated the acquisition of data within the limited timeframe prior to the procedure; it was a less objective assessment compared to a standardized nutritional questionnaire. Nevertheless, to the best of our knowledge, this is the first study looking at factors associated with colorectal neoplasia in an Australian setting. Although the lack of statistical difference might be due to the small sample size, the differences shown to be statistically significant add valuable information to the field and may help us better understand how these factors impact on different neoplastic lesions.

In conclusion, a significant association was found between the presence of neoplastic lesions and age≥65, T2DM, male gender and smoking. The predictors found for conventional adenomas (older age, male gender and smoking) were different from the predictors for neoplastic serrated polyps (T2DM and FHCRC).

CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest for this paper.

REFERENCES

1. IJspeert JE, Bossuyt PM, Kuipers EJ, et al. Smoking status informs about the risk of advanced serrated polyps in a screening population. *Endosc Int Open*. 2016;4(1):E73–78. doi: 10.1055/s-0034-1393361.
2. Aleksandrova K, Pischon T, Jenab M, et al. Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. *BMC medicine*. 2014;12:168. doi: 10.1186/s12916-014-0168-4.

3. Hang J, Cai B, Xue P, et al. The joint effects of lifestyle factors and comorbidities on the risk of colorectal cancer: a large chinese retrospective case-control study. *PLoS ONE*. 2015;10(12):e0143696. doi: 10.1371/journal.pone.0143696.
4. Marchand LL. Combined influence of genetic and dietary factors on colorectal cancer incidence in Japanese Americans. *JNCI Monographs*. 1999;1999(26):101–105. doi: 10.1093/oxfordjournals.jncimonographs.a024220.
5. O'Keefe SJ, Li JV, Lahti L, et al. Fat, fibre and cancer risk in African Americans and rural Africans. *Nature communications*. 2015;6:6342. doi: 10.1038/ncomms7342.
6. Luo S, Li JY, Zhao LN, et al. Diabetes mellitus increases the risk of colorectal neoplasia: an updated meta-analysis. *Clin Res Hepatol Gastroenterol*. 2016;40(1):110–123. doi: 10.1016/j.clinre.2015.05.021.
7. National Health and Medical Research Council. Nutrient Reference Values for Australia and New Zealand. Australia. https://www.nrv.gov.au/nutrients/dietary-fibre. Published September 2005. Accessed May 3, 2018.
8. Johnson CM, Wei C, Ensor JE, et al. Meta-analyses of colorectal cancer risk factors. *Cancer Causes Control.* 2013;24(6):1207–1222. doi: 10.1007/s10552-013-0201-5.
9. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. *JAMA*. 2008;300(23):2765–2778. doi: 10.1001/jama.2008.839.
10. 10. Limsui D, Vierkant RA, Tillmans LS, et al. Cigarette Smoking and Colorectal Cancer Risk by Molecularly Defined Subtypes. J Natl Cancer Inst. 2010;102(14):1012–1022. doi: 10.1093/jnci/djq201.
11. Fagunwa IO, Loughrey MB, Coleman HG. Alcohol, smoking and the risk of premalignant and malignant colorectal neoplasms. *Best Pract Res Clin Gastroenterol*. 2017;31(5):561–568. doi: 10.1016/j.bpg.2017.09.012.
12. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. *Clin Colon Rectal Surg*. 2009;22(4):191–197. doi: 10.1055/s-0029-1242458.
13. Figueiredo JC, Crockett SD, Snover DC, et al. Smoking-associated risks of conventional adenomas and serrated polyps in the colorectum. *Cancer Causes Control*. 2015;26(3):377–386. doi: 10.1007/s10552-014-0513-0.
14. Guraya SY. Association of type 2 diabetes mellitus and the risk of colorectal cancer: a meta-analysis and systematic review. *World J Gastroenterol*. 2015;21(19):6026–6031. doi: 10.3748/wjg.v21.i19.6026.
15. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst*. 2005;97(22):1679–1687. doi: 10.1093/jnci/dji375.
16. Yu F, Guo Y, Wang H, et al. Type 2 diabetes mellitus and risk of colorectal adenoma: a meta-analysis of observational studies. *BMC cancer*. 2016;16:642. doi: 10.1186/s12885-016-2685-3.
17. Tran TT, Naigamwalla D, Oprescu AI, et al. Hyperinsulinemia, but not other factors associated with insulin resistance, acutely enhances colorectal epithelial proliferation in vivo. *Endocrinology*. 2006;147(4):1830–1837. doi:10.1210/en.2005-1012.
18. La Vecchia C, Negri E, Decarli A, Franceschi S. Diabetes mellitus and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev*. 1997;6(12):1007–1010.
19. Berster JM, Goke B. Type 2 diabetes mellitus as risk factor for colorectal cancer. *Arch Physiol Biochem*. 2008;114(1):84–98. doi: 10.1080/13813450802008455.
20. Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. *Gastroenterology*. 2004;127(4):1044–1050. doi: 10.1053/j.gastro.2004.07.011.
21. National Diabetes Service Scheme. Diabetes in Australia. Australia. https://www.diabetesaustralia.com.au/diabetes-in-australia. Published 2015. Accessed May 3, 2018.
22. Australian Institute of Health and Welfare. Cancer compendium: information and trends by cancer type. https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/incidence-and-survival-by-stage. Published December 2018. Accessed July 10, 2019.
23. Zhou Q, Li K, Lin GZ, et al. Incidence trends and age distribution of colorectal cancer by subsite in Guangzhou, 2000–2011. *Chin J Cancer.* 2015;34(8):358–364. doi:10.1186/s40880-015-0026-6.
24. Gao RN, Neutel CI, Wai E. Gender differences in colorectal cancer incidence, mortality, hospitalizations and surgical procedures in Canada. *J Public Health (Oxf)*. 2008;30(2):194–201. doi:10.1093/pubmed/fdn019.
25. Kuipers EJ, Grady WM, Lieberman D, et al. Colorectal cancer. *Nat Rev Dis Primers*. 2015;1:15065. doi:10.1038/nrdp.2015.65.

Chapter 4

Effect of time of day and specialty on polyp detection rates in Australia

This chapter offers a brief summary of a paper published in the *Journal of Gastroenterology and Hepatology*. The statement of authorship and paper (.pdf) 'Effect of time of day and specialty on polyp detection rates in Australia' follow over the page.

4.1 Summary

This study investigated the effect of the time of day and the background of the endoscopist on the adenoma detection rate (ADR) and sessile serrated adenoma/polyp detection rates (SSA/P-DR) for screening colonoscopies. Research looking at the effect of fatigue among other professional-centred factors appears in several fields (e.g. medicine, aviation, motor vehicles). This is not different in the field of endoscopy, and studies into the effects of fatigue among endoscopists on medical outcomes have reported conflicting results for procedures conducted at the beginning of the workday compared to those at the end.

The contradictory findings might be related to the local settings in which the studies were conducted, as endoscopist/hospital-centred factors can vary for a number of reasons, including the particularities of training and medical practice in different countries. In the study reported here, we investigated how scheduling, as well as the background specialty of the endoscopist, influenced the detection of colorectal lesions in Australia. Our paper offers the first reported Australian data on this subject, and helps position Australia in the international literature exploring the effects of scheduling and training on the detection of colorectal lesions.

In this retrospective study, all colonoscopies performed at the Lyell McEwin Hospital (Adelaide, South Australia) for the year 2016 were analysed. The effect of time of day and endoscopist specialty on quality measures such as ADR and SSA/P-DR were assessed. In 2016, over 2500 colonoscopies were performed by nine gastroenterologists and six surgeons. The adjusted mean ADR for screening was found to be significantly higher when the procedure was carried out during the morning period (36.8% versus 30.5%). In addition, the same measure was also found to be significantly higher when a gastroenterologist performed the colonoscopy (36.8% versus 30.4%).

Although results in detection from both periods of the day and both background specialties saw the recommended standards in Australia achieved, the study results do provide clues on how the detection of neoplastic lesions during colonoscopy could be improved to boost the efficacy of screening programs.

4.2 Statement of authorship

Statement of Authorship

Title of Paper	Effect of time of day and specialty on polyp detection rates in Australia.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Effect of time of day and specialty on polyp detection rates in Australia. Zorron Cheng Tao Pu L, Lu K, Ovenden A, Rana K, Singh G, Krishnamurthi S, Edwards S, Wilson B, Nakamura M, Yamamura T, Ruszkiewicz A, Hirooka Y, Burt AD, Singh R. J Gastroenterol Hepatol. 2018 Dec 14. doi: 10.1111/jgh.14566. [Epub ahead of print] PMID: 30552716

Principal Author

Name of Principal Author (Candidate)	Leonardo Zorron Cheng Tao Pu
Contribution to the Paper	Conceptualised and designed the study. Involved in data collection, processing and statistical analysis. Interpreted the results and prepared the manuscript.
Overall percentage (%)	80%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 26/03/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Kevin Lu
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ENDOSCOPY

Effect of time of day and specialty on polyp detection rates in Australia

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Key words
adenoma, colonic neoplasms, colonic polyps, colonoscopy, personnel scheduling and staffing.

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Abstract

Background and Aim: Adenoma detection rate (ADR) is an important quality metric in colonoscopy. However, there is conflicting evidence around factors that influence ADR. This study aims to investigate the effect of time of day and endoscopist background on ADR and sessile serrated adenoma/polyp detection rate (SSA/P-DR) for screening colonoscopies.

Methods: Consecutive patients undergoing colonoscopy in 2016 were retrospectively evaluated. Primary outcome was the effect of time of day and endoscopist specialty on screening ADR. Secondary outcomes included evaluation of the same factors on SSA/P-DR and other metrics and collinearity of ADR and SSA/P-DR. Linear regression models were used for association between ADR, time of day, and endoscopist background. Bowel preparation, endoscopist, session, patient age, and gender were adjusted for. Linear regression model was also used for comparing ADR and SSA/P-DR. Chi-square was used for difference of proportions.

Results: Two thousand six hundred fifty-seven colonoscopies, of which 558 were screening colonoscopies, were performed. The adjusted mean ADR (screening) was 36.8% in the morning compared with 30.5% in the afternoon ($P < 0.0001$) and was 36.8% for gastroenterologists compared with 30.4% for surgeons ($P < 0.0001$). For every 1-h delay in commencing the procedure, there was a reduction in mean ADR by 3.4%. Using a linear regression model, a statistically significant positive association was found between ADR and SSA/P-DR ($P < 0.0001$).

Conclusions: Morning and afternoon sessions and gastroenterologists and surgeons achieved the minimum standards recommended for ADR. Afternoon lists and surgeons were associated with a lower ADR compared with morning and gastroenterologists, respectively. Additionally, SSA/P-DR showed collinearity with ADR.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer deaths in Australia.[1] CRC usually develops going through various known stages. CRC most commonly arises from colorectal polyps (CPs), although not every CP has precancerous features. Several histological types (e.g. inflammatory and hamartomatous) are not associated with CRC.[2] On the other hand, adenomatous polyps, sessile serrated adenomas/polyps (SSA/Ps), and traditional serrated adenomas are thought to be responsible for almost all CRCs.[3]

The efficacy of screening colonoscopies for CRC depends on the detection of CRC and also on the removal of premalignant and early lesions. The proportion of screening colonoscopies with at least one histologically confirmed colorectal adenomatous lesion is known as the adenoma detection rate (ADR). ADR is an independent predictor for the risk of CRC following screening colonoscopy.[4,5] Therefore, ADR is a key quality assessment indicator, and values of less than 20% are associated with 10 times increased risk of interval CRC.[5] In line with this, the Gastroenterological Society of Australia has set the minimum standard for ADR at 25%.

Factors affecting ADR can be divided into two groups: patient-related factors that include age, gender, and BMI and endoscopy-related factors including withdrawal time, time of day, and endoscopist training.[6–8] According to some studies, 71–86% of interval CRCs could be attributed to endoscopy-related factors.[9,10] This is a worrisome finding that urges further investigation.

Several studies mostly from North America and Europe have investigated the influence of endoscopist specialty and time of day. Unfortunately, there are major differences in both workload and training in endoscopy between different countries.[11,12]

Literature investigating the effects of endoscopy-related factors on colonoscopy quality measures in the Asia–Pacific region, specifically in Australia, is scant. With growing incidence of CRC in this region, this information is of great importance as it would allow institutions to focus their efforts on optimizing CRC prevention. In this study, we aim to investigate the effect of time of day and endoscopist specialty on ADR and SSA/P-DR in an outpatient hospital setting in Australia.

Methods

Data collection. This is a retrospective study on the effect of the time of day and endoscopists' background on ADR. All consecutive patients undergoing colonoscopy from January 1 to December 31, 2016, were enrolled. The procedures were performed with Olympus 180/190 series colonoscopes (Olympus Australia Pty Ltd & Olympus New Zealand LTD). Flexisigmoidoscopies were excluded from our cohort.

Data on all endoscopic procedures performed were initially retrieved from the endoscopic suite documentation system. Colonoscopies were filtered from this database and individually correlated with digitized versions of the procedure's final report. A clinical data information system was used to extract relevant clinical and pathology information. The earlier was then compiled into an electronic spreadsheet.

In our unit, patients are subjected to the "split" bowel preparation where they take half of the bowel preparation (i.e. 1 L of polyethylene glycol) on the previous day and the other half on the day of the procedure. For the procedure in the morning, the second half is taken at 5:00 AM in the morning for a procedural start time at 8:00 AM, and for a procedure in the afternoon, the second half is taken at 8:00 AM in the morning for a procedural start time at 1:00 PM.

Scheduling. The morning session is scheduled from 8:00 AM to 12:00 PM and the afternoon session from 1:00 PM to 5:00 PM. However, it is not uncommon for small delays in either commencing or completing procedures to occur. As such, patients were divided into morning and afternoon lists as per booking for analysis purposes. Within each session, the specific commencement recorded time was used. All procedures were performed by or under the supervision of an endoscopist certified by the Conjoint Committee for Recognition of Training in Gastrointestinal Endoscopy.

Analysis. Linear regression models were used to investigate the association between detection rates and various predictors, while adjusting for clustering on endoscopist (gastroenterologists and surgeons). Assumptions of a linear model were investigated and found to be upheld throughout. Bowel preparation (good/excellent *vs* average/fair/poor/inadequate), gender (male *vs* female), and age (< 60 *vs* ≥ 60 years old) were adjusted for in all models. Session (morning and afternoon) was adjusted for in models where endoscopist was a predictor. Main outcome consisted in the effects of time of day and endoscopist specialty on ADR for screening colonoscopies. Secondary outcomes included SSA/P detection rate (SSA/P-DR), proximal serrated polyp detection rate (PSP-DR), polyp detection rate (PDR), adenomas per patient (APP), and polyps per patient (PPP). Proximal colon was defined as cecum up to but not including the descending colon and was used for the calculation of PSP-DR and proximal ADR.

Adenoma detection rate was defined as the number of colonoscopies with at least one histologically confirmed adenomatous lesion. SSA/P-DR was considered as the number of procedures with at least one SSA/P. PSP-DR was defined as the number of procedures with at least one hyperplastic polyp or a traditional serrated adenoma or an SSA/P found in the proximal colon. PDR was the percentage of colonoscopies with any type of polyp found. PPP was the mean number of polyps found per positive colonoscopy (that had a polyp found). Similarly, APP is the mean of adenomatous lesions found per positive procedure. All but PDR and PPP were calculated based on the pathology report of the specific histology partnered with the colonoscopy report. PDR and PPP were based on the colonoscopy findings alone.

Further statistical analysis involved a linear regression model comparing ADR and SSA/P-DR. The statistical software used was SAS 9.4 (SAS Institute Inc., Cary, NC, USA). P value was considered statistically significant when < 0.01.

Results

Six surgeons and nine gastroenterologists performed 2657 colonoscopies, 558 of which were for colorectal screening. Cohort demographics can be found in Table 1. In summary, our cohort consisted in equally distributed men and women in their 60s, in which 2843 polyps were detected.

The adjusted ADR (for screening colonoscopies) was 36.8% in the morning session and 30.5% in the afternoon session. This difference was statistically significant ($P < 0.001$). Unexpectedly though, there was a significantly higher SSA/P-DR and PSP-DR in the afternoon (Table 2). There was also a statistically significant association between ADR and time as a continuous variable when

Table 1 Cohort demographics

Male patients, *n* (%)	1326 (49.9)
Patient age (years), mean (SD)	58.8 (14.5)
Colonoscopies for screening by gastroenterologists, *n* (%)	339 (60.8)
Colonoscopies for symptoms by gastroenterologists, *n* (%)	790 (55.4)
Colonoscopies for surveillance by gastroenterologists, *n* (%)	428 (63.6)
Polyp size (mm), mean (SD)	7.0 (7.7)
Right-sided polyps, *n* (%)	1302 (45.8)
Adenomas, *n* (%)	1501 (57.9)
Tubular adenomas, *n* (%)	1241 (47.9)
Tubulovillous adenomas, *n* (%)	243 (9.4)
Villous adenomas, *n* (%)	14 (0.5)
Serrated polyps, *n* (%)	829 (32.0)
Hyperplastic polyp, *n* (%)	474 (18.3)
Sessile serrated adenoma/polyp, *n* (%)	350 (13.5)
Traditional serrated adenoma, *n* (%)	5 (0.2)
Superficial cancer (up to submucosa), *n* (%)	10 (0.4)
Invasive cancer, *n* (%)	70 (2.7)
Insufficient material for analysis, *n* (%)	14 (0.5)
Normal mucosa, *n* (%)	120 (4.6)
Other, *n* (%)	48 (1.9)

Table 2 Adjusted ADR, SSA/P-DR, and PSP-DR comparison based on time of day

Indication	Outcome	Morning marginal means, % (95% CL)	Afternoon marginal means, % (95% CL)	Adjusted estimate (95% CI)	Adjusted *P* value
All	Adjusted ADR	32.5 (32.1, 33.0)	27.2 (26.7, 27.6)	5.35 (4.74, 5.96)	< 0.0001
All	Adjusted SSA/P-DR	6.6 (6.3, 6.8)	5.4 (5.2, 5.7)	2.25 (1.93, 2.58)	< 0.0001
All	Adjusted PSP-DR	5.5 (5.3, 5.7)	4.7 (4.5, 4.9)	0.81 (0.54, 1.08)	< 0.0001
Screening	Adjusted ADR	36.8 (36.6, 36.9)	30.5 (30.3, 30.6)	6.26 (6.07, 6.46)	< 0.0001
Screening	Adjusted SSA/P-DR	5.7 (5.6, 5.8)	6.2 (6.1, 6.3)	−0.49 (−0.61, −0.37)	< 0.0001
Screening	Adjusted PSP-DR	3.3 (3.2, 3.4)	4.9 (4.9, 5.0)	−1.63 (−1.72, −1.54)	< 0.0001

All models have been adjusted for session/endoscopist (depending on the predictor), age, gender, and bowel preparation.
ADR, adenoma detection rate; CI, confidence interval; CL, confidence level; PSP-DR, proximal serrated polyp detection rate; SSA/P-DR, sessile serrated adenoma/polyp detection rate.

adjusted for cofactors ($P < 0.001$). For every 1-h delay in commencing the procedure, there is a reduction in mean ADR by 3.4% (exponentiated estimate = 0.966, 95% confidence interval: 0.960, 0.972).

Using the screening data, the adjusted mean ADR for gastroenterologists was 36.8%. For surgeons, the mean ADR was 30.4%. There was a statistically significant difference between the two groups. The SSA/P-DR and PSP-DR were also significantly higher for gastroenterologists (Table 3). A statistically significant, positive association between ADR and SSA/P-DR was also found ($P < 0.001$). The individual contribution of each covariate for ADR, SSA/P-DR, and PSP-DR for all indications and screening subset is presented in Appendix A.

The PDR for screening colonoscopies in the morning and afternoon and for gastroenterologists and surgeons were 50.7% and 45.2% and 50.1% and 43.4%, respectively. These did not reach statistically significant difference. The mean PPP and APP were 2.26 and 1.88, respectively. These were also not statistically different among the different groups.

In the original analysis, there were 87 procedures where bowel preparation was not reported in neither the electronic database nor the digitalized final reports. As a result, the images from these colonoscopies were retrieved, and 79 of these procedures had their bowel preparations scored by the research team based on photographs. There were eight cases where there were insufficient images to make a comment. In a single case, the procedural report was not available. The final bowel preparation score can be found in Table 4.

Discussion

Primary outcomes

Time of day. The concept of fatigue affecting performance has been described in various nonmedical (pilots and truck drivers) and medical studies (anesthesiologists and surgeons).[13,14] There is currently no consensus on whether the scheduling of endoscopy impacts ADR.

Several studies in the USA have concluded that scheduling does not affect ADR.[15–19] Conversely, other studies in the USA,[20,21] Singapore,[22] and Canada[23] found that colonoscopies performed later in the day had a less favorable ADR. There had previously been no such studies in Australia.

Our study showed a higher ADR in the morning compared with the afternoon, with every increase in hour of commencing the procedure corresponding to a decrease in ADR. However, when compared the first and second blocks of either morning or afternoon, the statistical significance did not appear. This could be interpreted as although an overall "tiredness" affects the endoscopists, this only takes the leap of statistical significance after lunchtime.

We understand that the relationship between time of day and ADR could be attributed to several factors, including bowel preparation and endoscopist fatigue. After controlling for bowel preparation as a confounding factor, we were able to identify a statistically significant difference in the ADR between morning and afternoon lists. We postulate that the difference found could be due to fatigue.

Table 3 Adjusted ADR, SSA/P-DR, and PSP-DR comparison based on endoscopist specialty

Indication	Outcome	Gastroenterologist marginal means, % (95% CL)	Surgeon marginal means, % (95% CL)	Adjusted estimate (95% CI)	Adjusted *P* value
All	Adjusted ADR	30.0 (36.7, 36.9)	29.7 (29.3, 30.2)	0.22 (−0.41, 0.86)	0.491
All	Adjusted SSA/P-DR	7.1 (6.9, 7.3)	4.9 (4.6, 5.1)	2.25 (1.93, 2.58)	< 0.0001
All	Adjusted PSP-DR	6.7 (6.5, 6.9)	3.6 (3.4, 3.8)	3.09 (2.81, 3.37)	< 0.0001
Screening	Adjusted ADR	36.8 (36.7, 36.9)	30.4 (30.3, 30.6)	6.36 (6.15, 6.57)	< 0.0001
Screening	Adjusted SSA/P-DR	6.4 (6.3, 6.5)	5.5 (5.4, 5.6)	0.94 (0.81, 1.06)	< 0.0001
Screening	Adjusted PSP-DR	5.5 (5.4, 5.5)	2.8 (2.7, 2.9)	2.69 (2.59, 2.78)	< 0.0001

All models have been adjusted for session/endoscopist (depending on the predictor), age, gender, and bowel preparation.
ADR, adenoma detection rate; CL, confidence level; CI, confidence interval; PSP-DR, proximal serrated polyp detection rate; SSA/P-DR, sessile serrated adenoma/polyp detection rate.

Table 4 Cohort bowel preparation

Bowel preparation group, *n* (%)	Excellent	Good	Average or fair	Poor or inadequate	N/A
Morning	71 (5.5)	710 (55.5)	396 (30.9)	97 (7.6)	6 (0.5)
Afternoon	111 (8.1)	792 (57.5)	356 (25.9)	115 (8.4)	3 (0.2)
Gastroenterologists	81 (5.2)	1066 (68.5)	271 (17.4)	137 (8.8)	2 (0.1)
Surgeons	101 (9.2)	436 (39.6)	481 (43.7)	75 (6.8)	7 (0.6)
Patients with polyps	60 (4.8)	715 (56.9)	411 (32.7)	68 (5.4)	3 (0.2)
Patients without polyps	122 (8.7)	787 (56.2)	341 (24.4)	144 (10.3)	6 (0.4)
All patients	182 (6.8)	1502 (56.5)	752 (28.3)	212 (8.0)	9 (0.3)

N/A, not available.

Endoscopist background. While some studies have shown that colonoscopies performed by non-gastroenterologists result in higher interval CRC,[7,24] other studies have failed to show such a difference.[25,26] This could be explained if taken into account that the results from one country cannot be easily translated to another because of regional differences in training programs and requirements to practice as an endoscopist. Such heterogeneity highlights the importance of having studies looking at this same question in different settings.

Our study showed that in our Australian Centre, gastroenterologists had a higher ADR for screening colonoscopies than surgeons. This was sustained for SSA/P-DR and PSP-DR for screening colonoscopies as well. The only other study in Australia that looked at endoscopists' background influence in detection of polyps has small numbers and has found no significant difference in detection between gastroenterologists and colorectal surgeons.[27] Another difference from our study is that they have reported adenoma detection in colonoscopies for all indications, rather than ADR for screening colonoscopies, which is the known measure associated with CRC prevention.[4] Although their reported overall ADR for gastroenterologists and colorectal surgeons was similar (34% and 34.7%, respectively), their screening ADR was notably different (52.2% and 30%, respectively). This was found not statistically significant but likely due the small sample size (around 45 screening colonoscopies in total). Another difference to our study is that our surgeon arm does not consist solely of specialized colorectal surgeons. This may be a cause for the ADR difference.

Some proposed hypotheses to explain the difference in ADR between surgeons and gastroenterologists include subtle differences in approach to training, personality nuances, volume of procedures during and after surgical training, time constraints, increased fatigue because of more physically requiring surgical procedures, and differences in bowel preparation. In our study, there was a statistically significant higher proportion of patients with poor/average bowel preparation reported in the surgeons' list ($P < 0.001$). Nonetheless, the bowel preparation protocol is supposed to be standard split dose polyethylene glycol for all.

Secondary outcomes. The ADR has been criticized for being imprecise as sole indicator of quality during colonoscopy, firstly because the detection of just one adenoma is sufficient to qualify a colonoscopy as being of high quality as per the ADR, what could lead to gaming (known as "one and done"). Thus, in our study, we calculated the PPP and APP, which were 2.26 and 1.88, respectively. These did not differ among the groups.

Secondly, ADR imprecision as sole quality measure is due to the recent awareness of other histological types leading to cancer. It has been long thought that adenomas were the only precursors to CRC. However, the ADR only accounts for one of the two major pathways that lead to CRC, which is why we decided to look into SSA/P-DR as well. Recent research has shown that serrated polyps are responsible for up to 15–30% of all CRCs.[28,29] However, the pathological diagnosis of SSA/P is problematic.[30] As SSA/Ps are predominantly found in the proximal colon,[31] a metric that mitigate the pathological dilemma (hyperplastic polyp *vs* SSA/P) was created, the PSP-DR.

Kahi *et al.*[32] and IJspeert *et al.*[33] found that the ADR and PSP-DR were strongly correlated. The linear regression model in our study also showed a statistically significant association between ADR and serrated lesions but through SSA/P-DR ($P < 0.001$). This indicates that our endoscopists are removing both adenomatous and serrated neoplastic polyps, comprehensively protecting our patients from CRC. The confirmation of the correlation between detection (and removal) of neoplastic adenomatous and serrated lesions is rather important. If the ADR is not positively correlated with the PSP-DR and/or SSA/P-DR with a given endoscopist/hospital, it may indicate that serrated lesions are being missed/neglected during colonoscopies. Hence, although a collinearity has been shown in our data, we do not advocate in using only ADR as a quality measure.

The SSA/P-DR and PSP-DR found in our cohort were 6% and 4% for screening colonoscopies, which is consistent with the literature.[34] As opposed to ADR, SSA/P-DR and PSP-DR were increased in the afternoon session. We can postulate that the difference between the "runoff" time of the morning (3 h) and afternoon (5 h) preparations could have led to the reformation of the mucous cap and hence an increase in the detection of SSA/Ps in the afternoon. It is possible that the effect of the presence of a mucous cap surpassed the effect of the fatigue. The mucous cap feature is known to be important for SSA/P's detection and characterization, as opposed to adenomas.[35,36] Although it is known that a bad bowel preparation (e.g. below 5 in the Boston Bowel Preparation Scale—according to Lai *et al.*[37]) decreases the detection of polyps, a slightly suboptimal bowel preparation might have the opposite effect. Although not statistically significant, Anderson *et al.*[38] showed a trend of a higher detection of serrated lesions with a slightly "worse" bowel preparation (e.g. from excellent to good preparation). We postulate that the slightly higher percentage of excellent bowel preparation for screening colonoscopies in the morning (6.6% *vs* 4.3%) could explain the 0.5% higher SSA/P-DR in the afternoon. However, this difference was

not statistically significant ($P = 0.23$). Hence, although it is conceivable that SSA/P-DR may be negatively affected by fatigue the same way as ADR, this might be counterbalanced by a suboptimal bowel preparation that allows the formation of a mucous cap and hence draw the attention of the endoscopist. This could correspond to the findings in our cohort.

Limitations. There are some limitations to our study. It is a single-center study, and hence, the results may not be generalizable. However, most public Australian hospitals have similar patient and doctor cohorts and working conditions.

Because of the retrospective nature of this study, we were limited to calculate the cecal intubation rate, completion time, and withdrawal time. However, we can assume that the cecal intubation rate was above 95% for all of our endoscopists as they have been certified by the Gastrointestinal Society of Australia's "Colonoscopy Recertification Program." In addition, all of our colonoscopies were allocated for 30 min, indicating that adequate completion time was available to endoscopists to allow the minimum withdrawal time (6–10 min) to be routinely achieved.

Although usually a retrospective design would be considered a limitation in this scenario, we believe it might be an advantage as it allows to more accurately gauge the "true" ADR. If performed prospectively, endoscopists would be aware that their ADRs are being recorded. It may therefore cause them to become more diligent than normal and hence artificially inflate the detection of CPs during the period of the study.

The quality of bowel preparation was reported subjectively by endoscopists as inadequate, poor, fair, average, good, or excellent. Unfortunately, a more objective scale such as the Boston Bowel Preparation Scale was not used in our unit at that time. As such, there is likely variation between endoscopists.

We did not investigate the potential reasons behind the decline in ADR in the afternoon. Several possible factors have been postulated including physician fatigue, an urgency to finish work for the day, or more time constraints on the afternoon lists from delays in the morning or emergency endoscopy add-ons. These factors should be investigated in further studies.

In summary, our findings suggest we could potentially achieve better results with our screening colonoscopies if their schedule shift towards an early time in the day. However, the viability and practicability of such proposal need to be considered on a hospital by hospital basis.

Conclusion

In conclusion, regardless of endoscopy training or time of day, the minimum standards for ADR in screening colonoscopies were met. Nonetheless, afternoon lists and surgeons were associated with lower detection rates when compared with morning lists and gastroenterologists, respectively. SSA/P-DR was significantly associated with ADR and could be used as an additional measure of quality for colonoscopies.

References

1 Australian Institute of Health and Welfare. Cancer compendium: information and trends by cancer type. 2018.
2 Abu Dayyeh BK, Thosani N, Konda V *et al*. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting real-time endoscopic assessment of the histology of diminutive colorectal polyps. *Gastrointest. Endosc.* 2015; **81**: e1–6.
3 Bettington M, Walker N, Clouston A, Brown I, Leggett B, Whitehall V. The serrated pathway to colorectal carcinoma: current concepts and challenges. *Histopathology.* 2013; **62**: 367–86.
4 Corley DA, Jensen CD, Marks AR *et al*. Adenoma detection rate and risk of colorectal cancer and death. *N. Engl. J. Med.* 2014; **370**: 1298–306.
5 Kaminski MF, Regula J, Kraszewska E *et al*. Quality indicators for colonoscopy and the risk of interval cancer. *N. Engl. J. Med.* 2010; **362**: 1795–803.
6 Waldmann E, Regula J, Ferlitsch M. How can screening colonoscopy be optimized? *Dig. Dis.* 2015; **33**: 19–27.
7 Cooper GS, Xu F, Barnholtz Sloan JS, Schluchter MD, Koroukian SM. Prevalence and predictors of interval colorectal cancers in medicare beneficiaries. *Cancer* 2012; **118**: 3044–52.
8 Rex DK. Polyp detection at colonoscopy: endoscopist and technical factors. *Best Pract. Res. Clin. Gastroenterol.* 2017; **31**: 425–33.
9 le Clercq CM, Bouwens MW, Rondagh EJ *et al*. Postcolonoscopy colorectal cancers are preventable: a population-based study. *Gut* 2014; **63**: 957–63.
10 Pohl H, Robertson DJ. Colorectal cancers detected after colonoscopy frequently result from missed lesions. *Clin. Gastroenterol. Hepatol.* 2010; **8**: 858–64.
11 Bisschops R, Wilmer A, Tack J. A survey on gastroenterology training in Europe. *Gut* 2002; **50**: 724–9.
12 Patel K, Rajendran A, Faiz O *et al*. An international survey of polypectomy training and assessment. *Endosc. Int. Open.* 2017; **5**: E190–7.
13 Howard SK, Rosekind MR, Katz JD, Berry AJ. Fatigue in anesthesia: implications and strategies for patient and provider safety. *Anesthesiology* 2002; **97**: 1281–94.
14 Philip P, Taillard J, Sagaspe P *et al*. Age, performance and sleep deprivation. *J. Sleep Res.* 2004; **13**: 105–10.
15 Lurix E, Hernandez AV, Thoma M, Castro F. Adenoma detection rate is not influenced by full-day blocks, time, or modified queue position. *Gastrointest. Endosc.* 2012; **75**: 827–34.
16 Leffler DA, Kheraj R, Bhansali A *et al*. Adenoma detection rates vary minimally with time of day and case rank: a prospective study of 2139 first screening colonoscopies. *Gastrointest. Endosc.* 2012; **75**: 554–60.
17 Freedman JS, Harari DY, Bamji ND *et al*. The detection of premalignant colon polyps during colonoscopy is stable throughout the workday. *Gastrointest. Endosc.* 2011; **73**: 1197–206.
18 Munson GW, Harewood GC, Francis DL. Time of day variation in polyp detection rate for colonoscopies performed on a 3-hour shift schedule. *Gastrointest. Endosc.* 2011; **73**: 467–75.
19 Subramanian S, Psarelli EE, Collins P *et al*. Colonoscopy performance is stable during the course of an extended three-session working day. *Endosc. Int. Open.* 2015; **3**: E494–500.
20 Sanaka MR, Deepinder F, Thota PN, Lopez R, Burke CA. Adenomas are detected more often in morning than in afternoon colonoscopy. *Am. J. Gastroenterol.* 2009; **104**: 1659–64 quiz 65.
21 Vicari J. The influence of timing of colonoscopy on adenoma detection: is timing everything? *Am. J. Gastroenterol.* 2009; **104**: 1666–7.
22 Teng TY, Khor SN, Kailasam M, Cheah WK, Lau CC. Morning colonoscopies are associated with improved adenoma detection rates. *Surg. Endosc.* 2016; **30**: 1796–803.
23 Almadi MA, Sewitch M, Barkun AN, Martel M, Joseph L. Adenoma detection rates decline with increasing procedural hours in an endoscopist's workload. *Can. J. Gastroenterol. Hepatol.* 2015; **29**: 304–8.

24 Rabeneck L, Paszat LF, Saskin R. Endoscopist specialty is associated with incident colorectal cancer after a negative colonoscopy. *Clin. Gastroenterol. Hepatol.* 2010; **8**: 275–9.
25 Kozbial K, Reinhart K, Heinze G *et al*. High quality of screening colonoscopy in Austria is not dependent on endoscopist specialty or setting. *Endoscopy* 2015; **47**: 207–16.
26 Singh H, Nugent Z, Demers AA, Bernstein CN. Rate and predictors of early/missed colorectal cancers after colonoscopy in Manitoba: a population-based study. *Am. J. Gastroenterol.* 2010; **105**: 2588–96.
27 Lee AHH, Lojanapiwat N, Balakrishnan V, Chandra R. Is there a difference in adenoma detection rates between gastroenterologists and surgeons? *World J. Gastroi. Endoscopy.* 2018; **10**: 109–16.
28 Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology* 2007; **50**: 113–30.
29 Samowitz WS, Albertsen H, Herrick J *et al*. Evaluation of a large, population-based sample supports a CpG island methylator phenotype in colon cancer. *Gastroenterology* 2005; **129**: 837–45.
30 Benedict M, Galvao Neto A, Zhang X. Interval colorectal carcinoma: an unsolved debate. *World J. Gastroenterol.* 2015; **21**: 12735–41.
31 Yang JF, Tang SJ, Lash RH, Wu R, Yang Q. Anatomic distribution of sessile serrated adenoma/polyp with and without cytologic dysplasia. *Arch. Pathol. Lab. Med.* 2015; **139**: 388–93.
32 Kahi CJ, Hewett DG, Norton DL, Eckert GJ, Rex DK. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. *Clin. Gastroenterol. Hepatol.* 2011; **9**: 42–6.
33 IJspeert JE, van Doorn SC, van der Brug YM, Bastiaansen BA, Fockens P, Dekker E. The proximal serrated polyp detection rate is an easy-to-measure proxy for the detection rate of clinically relevant serrated polyps. *Gastrointest. Endosc.* 2015; **82**: 870–7.
34 East JE, Atkin WS, Bateman AC *et al*. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. *Gut* 2017; **66**: 1181–96.
35 IJspeert JE, Bastiaansen BA, van Leerdam ME *et al*. Development and validation of the WASP classification system for optical diagnosis of adenomas, hyperplastic polyps and sessile serrated adenomas/polyps. *Gut* 2016; **65**: 963–70.
36 Pu L, Cheong KL, Koay DSC *et al*. Randomised controlled trial comparing modified Sano's and narrow band imaging international colorectal endoscopic classifications for colorectal lesions. *World J. Gastroi. Endoscopy.* 2018; **10**: 210–8.
37 Lai EJ, Calderwood AH, Doros G, Fix OK, Jacobson BC. The Boston Bowel Preparation Scale: a valid and reliable instrument for colonoscopy-oriented research. *Gastrointest. Endosc.* 2009; **69**: 620–5.
38 Anderson JC, Butterly L, Robinson CM, Goodrich M, Weiss JE. Impact of fair bowel prep on adenoma and serrated polyp detection: data from the New Hampshire Colonoscopy Registry using a standardized preparation quality rating. *Gastrointest. Endosc.* 2014; **80**: 463–70.

A. Appendix

Table A1 Difference of marginal means for ADR *versus* session and confounders, for all data

Outcome	Covariate	Comparison	Estimate (95% CI)	*P* value
ADR	Session	1 *vs* 2	5.35 (4.74, 5.96)	< 0.0001
	Bowel preparation	Average/fair/poor/inadequate *vs* good/excellent	−0.79 (−1.44, −0.13)	0.0186
	Gender	Female *vs* male	−1.00 (−1.61, −0.40)	0.0012
	Age	< 60 *vs* ≥ 60 years old	−3.52 (−4.13, −2.90)	< 0.0001
	Endoscopist background	Gastroenterology *vs* surgery	0.22 (−0.41, 0.86)	0.4899

ADR, adenoma detection rate; CI, confidence interval.

Table A2 Difference of marginal means for ADR *versus* session and confounders, for screening data

Outcome	Covariate	Comparison	Estimate (95% CI)	*P* value
ADR	Session	1 *vs* 2	6.26 (6.07, 6.46)	< 0.0001
	Bowel preparation	Average/fair/poor/inadequate *vs* good/excellent	0.16 (−0.06, 0.38)	0.1562
	Gender	Female *vs* male	0.11 (−0.08, 0.31)	0.2625
	Age	< 60 *vs* ≥ 60 years old	0.04 (−0.16, 0.23)	0.7134
	Endoscopist background	Gastroenterology *vs* surgery	6.36 (6.15, 6.56)	< 0.0001

ADR, adenoma detection rate; CI, confidence interval.

Table B1 Difference of marginal means for SSA/P-DR *versus* session and confounders, for all data

Outcome	Covariate	Comparison	Estimate (95% CI)	*P* value
SSA/P-DR	Session	1 *vs* 2	1.14 (0.83, 1.45)	< 0.0001
	Bowel preparation	Average/fair/poor/inadequate *vs* good/excellent	−0.34 (−0.67, −0.00)	0.0468
	Gender	Female *vs* male	−0.63 (−0.94, −0.32)	< 0.0001
	Age	< 60 *vs* ≥ 60 years old	−1.56 (−1.87, −1.24)	< 0.0001
	Endoscopist background	Gastroenterology *vs* surgery	2.25 (1.93, 2.58)	< 0.0001

CI, confidence interval; SSA/P-DR, sessile serrated adenoma/polyp detection rate.

Table B2 Difference of marginal means for SSA/P-DR *versus* session and confounders, for screening data

Outcome	Covariate	Comparison	Estimate (95% CI)	*P* value
SSA/P-DR	Session	1 *vs* 2	−0.49 (−0.61, −0.37)	< 0.0001
	Bowel preparation	Average/fair/poor/inadequate *vs* good/excellent	−0.10 (−0.23, 0.04)	0.1562
	Gender	Female *vs* male	−0.07 (−0.18, 0.05)	0.2625
	Age	< 60 *vs* ≥ 60 years old	−0.02 (−0.14, 0.10)	0.7134
	Endoscopist background	Gastroenterology *vs* surgery	0.94 (0.81, 1.06)	< 0.0001

CI, confidence interval; SSA/P-DR, sessile serrated adenoma/polyp detection rate.

Table C1 Difference of marginal means for PSP-DR *versus* session and confounders, for all data

Outcome	Covariate	Comparison	Estimate (95% CI)	*P* value
PSP-DR	Session	1 *vs* 2	0.81 (0.54, 1.08)	< 0.0001
	Bowel preparation	Average/fair/poor/inadequate *vs* good/excellent	−0.13 (−0.42, 0.16)	0.3648
	Gender	Female *vs* male	−0.55 (−0.82, −0.28)	< 0.0001
	Age	< 60 *vs* ≥ 60 years old	−1.34 (−1.61, −1.06)	< 0.0001
	Endoscopist background	Gastroenterology *vs* surgery	3.09 (2.81, 3.37)	< 0.0001

CI, confidence interval; PSP-DR, proximal serrated polyp detection rate.

Table C2 Difference of marginal means for PSP-DR *versus* session and confounders, for screening data

Outcome	Covariate	Comparison	Estimate (95% CI)	*P* value
PSP-DR	Session	1 *vs* 2	−1.63 (−1.72, −1.54)	< 0.0001
	Bowel preparation	Average/fair/poor/inadequate *vs* good/excellent	−0.07 (−0.18, 0.03)	0.1562
	Gender	Female *vs* male	−0.05 (−0.14, 0.04)	0.2625
	Age	< 60 *vs* ≥ 60 years old	−0.02 (−0.11, 0.07)	0.7134
	Endoscopist background	Gastroenterology *vs* surgery	2.69 (2.59, 2.78)	< 0.0001

CI, confidence interval; PSP-DR, proximal serrated polyp detection rate.

Chapter 5

Polyp detection rate as a surrogate for adenoma and sessile serrated adenoma/polyp detection rates

This chapter offers a brief summary of a paper published in *Gastrointestinal Tumors*, along with supplementary materials. The statement of authorship and a copy of the paper 'Polyp detection rate as surrogate for adenoma and sessile serrated adenoma/polyp detection rates' follow over the page.

5.1 Summary

A commonly used quality measure for colonoscopy is the adenoma detection rate (ADR). The ADR, calculated on a per-endoscopist basis, can be used to monitor minimum standards of practice as it has been directly associated with interval CRC and CRC mortality. However, as tracking polyp histology is time-consuming, it is unlikely ADR will be widely used in clinical practice as a measure of quality.

A simpler measure for monitoring quality in colonoscopy would be the polyp detection rate (PDR), which can be used as a surrogate for the ADR. As opposed to the ADR, the PDR does not require a follow-up histology on each resected polyp. In the study presented here, we retrospectively assessed colonoscopy quality measures (i.e. ADR and SSA/P-DR) and determined their association through quotients (ADQ and SSA/P-DQ respectively). Although the development of quotients for using PDR as a surrogate for ADR has been proposed before, it is uncertain whether quotients could be used in different countries. Given the idiosyncratic nature of medical training and practice in different countries, our research using Australian data becomes relevant and contributes to the body of knowledge.

In this study, our data consisted of all colonoscopies performed at the Lyell McEwin Hospital (Adelaide, South Australia) in 2016. The data were analysed month by month for ADR and SSA/P-DR and their correlation with PDR. The goal of the research was to determine an adenoma detection quotient (ADQ) for the cohort and evaluate the number of procedures required for the ADQ to become stable. The ADQ value (0.68) was consistent with other studies and stabilised after 500 procedures. An excellent interclass correlation coefficient between actual and predicted ADR was found for every endoscopist who had performed over 177 endoscopies during the year 2016.

This study highlights the potential of the ADQ to make it possible to use the PDR instead of the ADR as a quality measure to be monitored by the specialty societies, regulatory bodies and the endoscopists themselves.

5.2 Statement of authorship

Statement of Authorship

Title of Paper	Polyp detection rate as a surrogate for adenoma and sessile serrated adenoma/polyp detection rates
Publication Status	☑ Published ☑ ~~Accepted for Publication~~ ☐ ~~Submitted for Publication~~ ☐ Unpublished and Unsubmitted work written in manuscript style
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Principal Author

Name of Principal Author (Candidate)	Leonardo Zorron Cheng Tao Pu		
Contribution to the Paper	Conceptualised and designed the study. Involved in data collection, processing and statistical analysis. Interpreted the results and prepared the manuscript.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

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ii. permission is granted for the candidate in include the publication in the thesis; and

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Research Article

Polyp Detection Rate as a Surrogate for Adenoma and Sessile Serrated Adenoma/Polyp Detection Rates

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Keywords
Colonoscopy · Health metrics · Colonic polyps · Colonic neoplasms · Colorectal cancer

Abstract
Introduction: Quality measures for colonoscopy such as adenoma detection rate (ADR) have been proposed to be surveilled for ensuring minimum standards. However, its direct measurement is time consuming and often neglected. Extrapolating ADR and other quality measures from polyp detection rate (PDR) can be a pragmatic alternative. ***Objective:*** To determine quotients for estimating ADR and sessile serrated adenoma/polyp detection rate (SSA/P-DR) from PDR in an Australian cohort. ***Methods:*** Consecutive adult patient colonoscopies during a 1-year period were retrospectively assessed in a single Australian tertiary endoscopy center. Adenoma detection quotient (ADQ) and SSA/P detection quotient (SSA/P-DQ) were defined as the division of ADR and SSA/P-DR by PDR, respectively. The primary outcome was the number of procedures to achieve a stable cumulative ADQ and SSA/P-DQ. Secondary outcomes

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included evaluation of ADQ and SSA/P-DQ in different subsets. ***Results:*** In total, 2,657 colonoscopies were performed by 15 endoscopists in 2016. The ADR, SSA/P-DR, and PDR found were 32.2, 6.7, and 47.3%, respectively. The ADQ and SSA/P-DQ values found were 0.68 and 0.14, respectively. After approximately 500 procedures, both ADQ and SSA/P-DQ became stable. Interclass correlation coefficient (ICC) for the prediction of ADR from ADQ was excellent for all endoscopists that performed >177 procedures in that year (ICC 0.84). ***Conclusions:*** ADQ and SSA/P-DQ values were consistent when over 500 procedures were analyzed. ADQ had an excellent correlation with ADR when >177 procedures per endoscopist were evaluated.

Introduction

Colorectal cancer (CRC) ranks second in cancer deaths and third in incidence among all cancers in Australia. In 2018, there were approximately 17,000 new cases and 4,100 deaths due to CRC in the country [1]. According to the World Health Organization, a similar trend can be found throughout the world where CRC sits behind breast, prostate, and lung for incidence and behind lung and breast for mortality [2]. It is well known that CRC arises from either adenomas, SSA/polyps (SSA/Ps), or traditional serrated adenomas (TSAs) [3, 4]. Screening colonoscopy and subsequent removal of premalignant colorectal lesions (CLs) have been shown to prevent CRC [5–8]. As colonoscopy has become a standard procedure, quality measures have been investigated to monitor its efficacy. The adenoma detection rate (ADR) is defined as the number of patients with at least one adenoma divided by the number of screening colonoscopies is one of the most important quality measures. It has been shown that higher ADR is associated with lower mortality from CRC [9]. Currently, the Gastroenterological Society of Australia recommends an ADR of at least 25% [10]. In addition to monitoring adenomatous lesions, the focus has also shifted recently to serrated lesions. SSA/Ps have been shown to contribute to up to 30% of CRCs, albeit having a much lower prevalence [11]. The serrated pathway has a higher risk for the development of CRC than the traditional adenoma-carcinoma pathway [12–14]. This may also be due to the difficulty in its detection or the misdiagnosis either during colonoscopy or pathological evaluation [15–17]. It may hence be useful to calculate an SSA/polyp detection rate (SSA/P-DR) in addition to the ADR.

Although calculating both the ADR and SSA/P-DR makes intuitive sense and could and perhaps should be used as a measure of quality, both measures have not been used widely possibly due to the additional effort required (tracking histology of every single polyp removed). Some studies have proposed the use of a quotient based on the polyp detection rate (PDR) to promptly predict the ADR, negating the need to track the final histology [18–21]. If consistent, the adoption of quotient values could enable swift calculation of ADR and SSA/P-DR for endoscopists and regulatory bodies, allowing for an effective performance evaluation tool. This study was designed to calculate and evaluate the stability of adenoma detection quotient (ADQ) and SSA/polyp detection quotient (SSA/P-DQ) over the period of one year.

Materials and Methods

Consecutive patients undergoing a colonoscopy at a tertiary Australian endoscopy center for any indication over a 12-month period were included (January to December 2016). This period was chosen based on the average number of colonoscopy procedures per year (~2,500), which was a similar number to the numbers from a similar American study [20]. An existing electronic database was interrogated, and all procedures labeled as "colonoscopy" were initially retrieved. Then, the final procedural reports were identified and separated into positive colonoscopies (i.e., with at least one CL found) and negative colonoscopies (i.e.,

Table 1. Polyp histology

Polyp histology	*n* (%)
No histology report	251 (8.8)
No tissue for analysis	25 (0.9)
Normal mucosa*	127 (4.5)
Adenomas	**1,501 (52.8)**
Tubular adenoma LGD	**1,236 (43.5)**
Tubular adenoma HGD	**8 (0.3)**
Tubulovillous adenoma LGD	**210 (7.4)**
Tubulovillous adenoma HGD	**33 (1.2)**
Villous adenoma LGD	**10 (0.4)**
Villous adenoma HGD	**4 (0.1)**
Serrated polyps	829 (29.2)
Hyperplastic	474 (16.7)
SSA/Ps without dysplasia	**323 (11.4)**
SSA/Ps with dysplasia	**27 (1.0)**
TSA	**5 (0.2)**
Superficial cancer**	**10 (0.4)**
Invasive cancer	**70 (2.5)**
Other (e.g., inflammatory, hamartoma)***	30 (1.1)

Neoplastic lesions in bold. * Normal mucosa included melanosis coli. ** Invasion of lamina propria invasion and muscularis mucosae, restricted to the submucosa. *** Only one lesion classified as "other" was neoplastic (ganglioneuroma). LGD, low-grade dysplasia; HGD, high-grade dysplasia; SSA/Ps, sessile serrated adenoma/polyps; TSA, traditional serrated adenomas.

no CL found). Procedures initially labeled as colonoscopies and found to be flexisigmoidoscopies or ileoscopies in the procedure reports were excluded. All colonoscopies were performed or supervised by a Gastroenterologist or Surgeon accredited for performing colonoscopies by the Conjoint Committee for Recognition of Training in Gastrointestinal Endoscopy. Pathology reports were collected using a patient clinical information database. The colonoscopes used for the procedures were from the Olympus® 180 and 190 series. The "split" bowel preparation method was used for bowel preparation (i.e., 1 L of polyethylene glycol on the previous day and 1 L on the day of the procedure). As the bowel cleanliness status was expected to affect in a similar way all polyp detection metrics (i.e., PDR, ADR and SSA/P-DR), poor bowel preparation was recorded but not used as inclusion/exclusion criteria.

Individual consent was waived by the Northern Adelaide Local Health Network human research Ethics Committee (HREC/16/TQEH/283) due to the retrospective nature of the study. Data on indication, bowel preparation, age, gender, polyp histology, and location of the polyp within the colon was retrieved.

The primary outcome was to analyze the cumulative ADQ and SSA/P-DQ within the 1-year period to determine at what point the value became consistent (i.e., within 1 SD). Secondary outcomes included the comparison of predicted ADR and SSA/P-DR with the actual ADR and SSA/P-DR and the evaluation of ADQ and SSA/P-DQ for screening and specialty subsets.

ADR, SSA/P-DR, and PDR were defined as the proportion of colonoscopies with at least one adenoma, SSA/P and polyp, respectively. ADR and SSA/P-DR were based on both colonoscopy findings and histology report while PDR comprised of colonoscopy findings alone. ADQ and SSA/P-DQ were defined as the division of ADR and SSA/P-DR, respectively, by PDR.

The χ^2 test was used for comparison of 2 proportions (for difference in detection rates between the first and last semesters) and the *t* test for comparison of means (for difference in quotients between the first and last trimesters). *p* value was considered significant when <0.05. Interclass correlation coefficient (ICC) was calculated with average measures and consistency of agreement through STATA software (©Copyright 1996–2019 StataCorp LLC); and interpreted according to Cicchetti et al. [22] (up to 0.40 = poor correlation; 0.40–0.59 = fair correlation; 0.60–0.74 = good correlation; and 0.75–1.00 = excellent correlation).

Table 2. ADQ and SSA/P-DQ for the whole year and first/last trimesters

Period of measurement (*n*)	ADR, %	SSA/P-DR, %	PDR, %	ADQ, %	SSA/P-DQ, %
Full cohort (2,657)	32.2	6.7	47.3	0.68	0.14
First 3 months (705)	34.6	7.4	51.1	0.68	0.14
Last 3 months (570)	31.9	6.7	47.7	0.67	0.14

ADR, adenoma detection rate; SSA/P-DR, sessile serrated adenoma/polyp detection rate; PDR, polyp detection rate; ADQ, adenoma detection quotient; SSA/P-DQ, sessile serrated adenoma/polyp detection quotient.

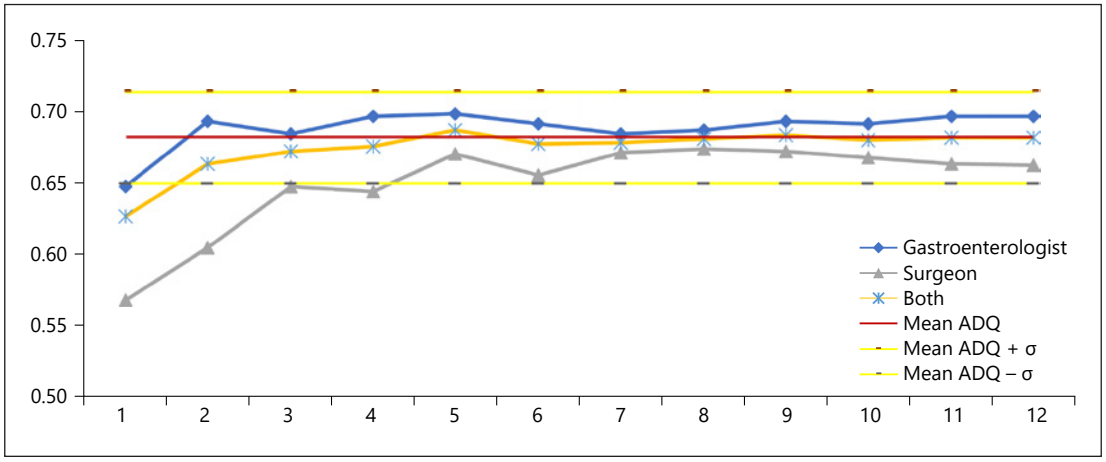

Fig. 1. Cumulative ADQ for all colonoscopies. ADQ, adenoma detection quotient.

Results

In total, 2,498 patients underwent 2,657 colonoscopies between January and December 2016. These procedures were performed by 9 gastroenterologists and 6 surgeons from a tertiary Australian endoscopy center. About 49.8% were males, and the mean age of the entire cohort was 58.6 years (SD 14.6). The bowel preparation for the whole cohort was excellent or good in 63.3%, average or fair in 28.3%, and poor or inadequate in 8.0%. In 9 procedures (0.3%), information on the bowel cleanliness state was not available. About 47.5% of the cohort was over 60 years of age. The mean diameter of the 2,843 polyps detected was 7 mm (SD 7.7). Detailed histology can be found in Table 1.

For the entire cohort, the ADR, SSA/P-DR, and PDR were 32.2, 6.7, and 47.3%, respectively. The difference in ADR, SSA/P-DR and PDR between the first and last semester was not statistically significant. The ADQ and SSA/P-DQ for the whole period was 0.68 and 0.14. This was not statistically different from when the ADQ and SSA/P-DQ were analyzed separately for the first and last trimesters and compared (Table 2).

The mean ADQ varied from 0.56 to 0.77 throughout the year for all indications and was similar between Gastroenterologists and Surgeons (0.69 and 0.66, respectively). SSA/P-DQ varied from 0.06 to 0.23 with similar pattern. The SD was 0.03 for both quotients.

Looking at cumulative curves, it was observed that the ADQ stabilized after the 2nd month for the whole cohort and after the 5th month for both subsets (gastroenterologists and surgeons, Fig. 1). The number of procedures necessary to reach stability for the full cohort

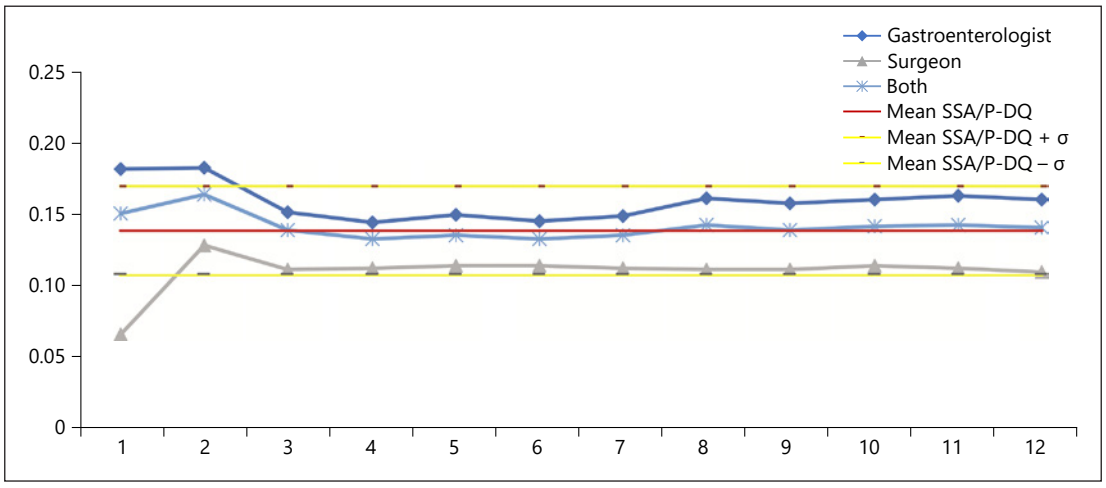

Fig. 2. Cumulative SSA/P-DQ for all colonoscopies. SSA/P-DQ, sessile serrated adenoma/polyp detection quotient.

Table 3. Individual results for predicted and actual adenoma and SSA/P-DR (high numbers group – all indications)

Endoscopist	1	2	3	4	5	6
Number	308	365	224	315	248	291
PDR, %	41.90	59.20	42.40	43.80	46.80	56.40
Predicted ADR, %	28.50	40.20	28.80	29.80	31.80	38.30
Actual ADR, %	30.50	45.20	26.80	31.40	26.60	38.80
Actual-predicted ADR gap, %	2.00	5.00	–2.10	1.60	–5.20	0.50
Predicted SSA/P-DR, %	5.90	8.30	5.90	6.10	6.50	7.90
Actual SSA/P-DR, %	7.10	11.20	6.70	8.60	5.60	5.20
Actual-predicted SSA/P-DR gap, %	1.30	2.90	0.80	2.40	–0.90	–2.70

ADR, adenoma detection rate; SSA/P-DR, sessile serrated adenoma/polyp detection rate; PDR, polyp detection rate.

was between 300 and 500, depending on the subsets analyzed. SSA/P-DQ also reached stability within the first 5 months (Fig. 2); with <500 procedures. Using the same ADQ and SSA/P-DQ, the subanalysis of screening dataset reached stability at a later timeframe but with similar total number of procedures (onlline suppl. Fig. 1 and 2; for all online suppl. material, see www.karger.com/doi/10.1159/000505622).

In order to evaluate the internal validity of our quotients, individual PDR, ADR, and SSA/P-DR were calculated. As no individual endoscopist was able to reach 500 colonoscopies during 2016, we have used all endoscopists that surpassed the average number of procedures for that year (i.e., 177 colonoscopies). Six endoscopists reached this mark, 4 gastroenterologists (endoscopists 1–4) and 2 surgeons (endoscopists 5 and 6). The mean of procedures per endoscopist was 292 in this subset. For these endoscopists, the ADQ and SSA/P-DQ were calculated and lead to a maximum variability of 5% between predicted and actual ADR and of 3% between predicted and actual SSA/P-DR (Table 3). For endoscopists that did not reach these numbers (mean number of procedures = 101), the variation between predicted and actual ADR was 14% and between predicted and actual SSA/P-DR was 7% (online suppl. Table 2). For the first group, there was an excellent correlation between actual and predicted ADR (ICC 0.84) but a poor correlation between actual and predicted SSA/P-DR (ICC 0.04).

Table 4. Pooled screening predicted and actual adenoma and SSA/P-DR

Screening colonoscopies	Gastro	Surgeon	All cohort
Number	339	219	558
PDR, %	50.10	43.40	47.50
Predicted ADR, %	34.10	29.50	32.30
Actual ADR, %	36.30	30.60	34.10
Actual-predicted ADR gap, %	2.20	1.10	1.80
Predicted SSA/P-DR, %	7.00	6.10	6.60
Actual SSA/P-DR, %	6.50	5.50	6.10
Actual-predicted SSA/P-DR gap, %	–0.50	–0.60	–0.60

ADR, adenoma detection rate; SSA/P-DR, sessile serrated adenoma/polyp detection rate; PDR, polyp detection rate.

However, when looking at only Gastroenterologists, this correlation was excellent (ICC 0.83). As no single endoscopist had done >100 screening colonoscopies in 2016, the pooled ADR and SSA/P-DR was analyzed for the screening subset. This showed excellent and good correlation between predicted and actual detection rates. The ICC for screening colonoscopies was 0.98 for ADR and 0.67 for SSA/P-DR (Table 4).

Discussion/Conclusion

One of the major quality measures presently proposed for monitoring endoscopists' performance is the ADR. Serrated polyps are an important precursor of CRC and hence another metric, the sessile SSA/P-DR, has been proposed. In order to track these metrics, a post-colonoscopy pathology assessment is required. This is time consuming and has been one of the main deterrent factors for widespread use of ADR and SSA/P-DR. The possibility of extrapolating the ADR and SSA/P-DR from a simple metric (PDR) could provide a more pragmatic alternative. Currently, no consensus values exist for the ADQ and the SSA/P-DQ due to potential for variation in different settings. The ADQ found in our study (i.e., 0.68) was consistent with what was found in recent studies from Murchie et al. [21] (i.e., 0.66–0.67) and Elhanafi et al. [20] (i.e., 0.68). This lends support to the use of this quotient in Australia.

In our study, the presence of a polyp in the colonoscopy was used for calculation of the PDR rather than the histology report, what is consonant with the concept of using PDR for predicting ADR. Therefore, even though 8.8% of the detected polyps did not have a histology report (mainly for not being resected due to benign features such as diminutive rectosigmoid HPs), this were still used as positive colonoscopies for calculating PDR. On the other hand, only histologically confirmed adenomas and SSA/Ps were used for calculating ADR and SSA/P-DR, respectively.

To the best of our knowledge, this is the first study describing the SSA/P-DQ. Although the study has shown a consistent internal validity similar to the ADQ, the correlation between predicted and actual SSA/P-DR was excellent only for gastroenterologists. This might be due to the relative lower SSA/P prevalence. Even with only 3% predicted-actual gap, this represented a wide relative variation and led to an important impact on correlation. Further studies are required to validate the usefulness of SSA/P-DQ, bearing in mind the diversity in SSA/P endoscopy and pathology diagnoses.

ADQ and SSA/P-DQ derived from the whole cohort were able to predict ADR and SSA/P-DR for individual endoscopists regardless of their specialty (i.e., Gastroenterology or Surgery). Therefore, the nonstatistically significant difference for the ADQ and SSA/P-DQ of the individual subsets does not seem to affect the use of detection quotients in endoscopy. We hypoth-

esize that this minor difference might be a product of a slightly higher detection of non-neoplastic polyps by the surgeons, or it might be due to random variation.

In a study from Amsterdam on 1,426 screen-naïve participants, the prevalence of HPs, SSA/Ps and TSAs was 23.8, 4.8, and 0.1%, respectively. Of the 1,782 specimens, 41.8% (744) were found to be SPs. Of those, 14.9% (111) were SSA/Ps [23]. These findings did not deviate much from the findings of our cohort where the overall prevalence of SSA/Ps was 12.4%. Among SPs, 57.2% were classified as HPs, 42.2% as SSA/Ps and 0.6% as TSAs. A Korean study found SSA/Ps in 3.1% of 1,375 asymptomatic patients over 50 years of age. The percentage of patients with adenomas was 43.5% [24]. These percentages were expected to be even higher as they evaluated only proximal colon polyps. In another study from the East, only 8.7% of CRCs were associated with the serrated pathway [25]. In addition to the setting, the time when the study is performed also matters. A study at the Mayo Clinic based on data from 2005 to 2007 found only 2.9% of polyps was SSA/Ps [26]. In contrast, another study in the USA found an overall prevalence of 8.1% and a prevalence of 15.8% in the last year of the study – 2012 [27]. It appears that the prevalence of SSA/Ps prevalence is higher in more recent studies. This may be a result of increased awareness of the entity and/or due to systematic removal of adenomas in the past, which could lead to a relative increase in SSA/P abundance.

The literature as well as our cohort support the belief of a higher SSA/P prevalence is present in western countries [28–32]. From the 701 diminutive RS polyps with confirmed tissue on histology, 305 were neoplastic (43.5%). Two hundred and twenty-six were adenomas (2 with high grade dysplasia), 77 SSA/Ps (3 with dysplasia) and 2 TSAs. Among serrated lesions, HPs corresponded to 81.4% of the diminutive polyps in the RS while SSA/Ps represented 18.2% (online suppl. Table 1). The SSA/P-DQ would most likely have greater applicability in Western countries. However, it is important to note that this study was designed focusing on detection quotients rather than detection rates. Therefore, the inclusion of patients with different medical backgrounds (e.g., previous CRC, variable family history of CRC and fecal occult blood test positive) warrants a critical view on the reported ADR and SSA/P-DR found.

A limitation of this study is the relatively small number of procedures per individual endoscopist. This is however an actual reflection of procedures performed by a range of endoscopists in a tertiary public hospital in the country. Nevertheless, when looking at endoscopists with >177 procedures, the prediction was accurate with an actual-predicted gap of at most 5% for ADR and 3% for SSA/P-DQ. A conservative policy could then be used to account for this variability. Future research for validation of these findings in other Australian centers is warranted.

In conclusion, ADQ and SSA/P-DQ values were consistent when over 500 procedures were analyzed. ADQ had an excellent correlation with ADR when >177 procedures per endoscopist were evaluated. The quotient values proposed for ADQ and SSA/P-DQ could be used for an easier calculation of endoscopists' ADR (0.68 × PDR) and SSA/P-DR (0.14 × PDR), potentially allowing for better evaluation of this important quality measure. As the Australian guidelines recommend that each Endoscopist has an ADR of at least 25%, a minimum PDR of 40% could be used as a surrogate marker. If this is not met, calculation of the actual ADR would be necessary. In addition, after an ideal SSA/P-DR is determined, SSA/P-DQ could then be used to measure this quality indicator.

Statement of Ethics

This study was approved by the Human Research Ethics Committee (TQEH/LMH/MH) under the reference number HREC/16/TQEH/283. Due to the retrospective nature of the study, the Committee has waived the requirement of individual written consents. This Committee is constituted in accordance with the NHMRC National Statement on Ethical Conduct in Human Research (2007) and incorporating all updates.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

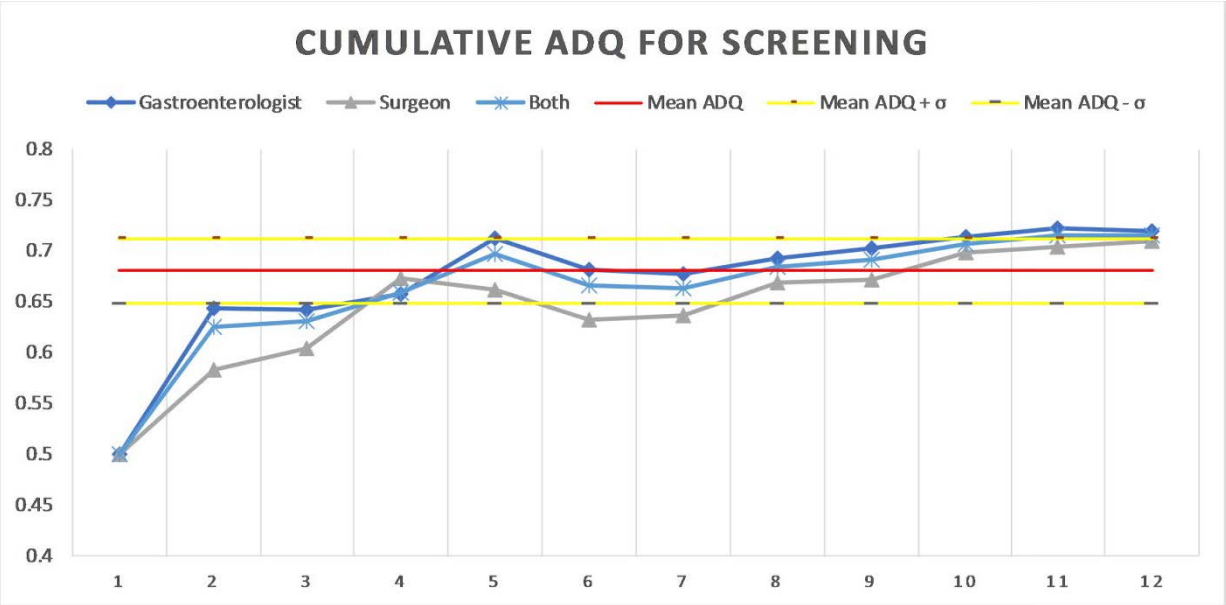
All authors have read and complied with author guidelines and contributed to this manuscript as described: L.Z.C.T.P., A.D.B., and R.S. conceptualized and designed the study. R.S. was responsible for the study supervision. L.Z.C.T.P., S.K., and A.O. were involved in the data extraction. L.Z.C.T.P., G.S., K.R., and S.E. were involved in the statistical analysis. L.Z.C.T.P., K.R., G.S., S.K., and A.O. drafted the manuscript. L.Z.C.T.P., M.N., T.Y., A.R., Y.H., and M.F. were involved in the interpretation of the results. A.D.B., R.S., M.N., T.Y., S.E., A.R., Y.H., and M.F. critically revised the manuscript for intellectual content. All authors read and approved the final version of this manuscript.

References

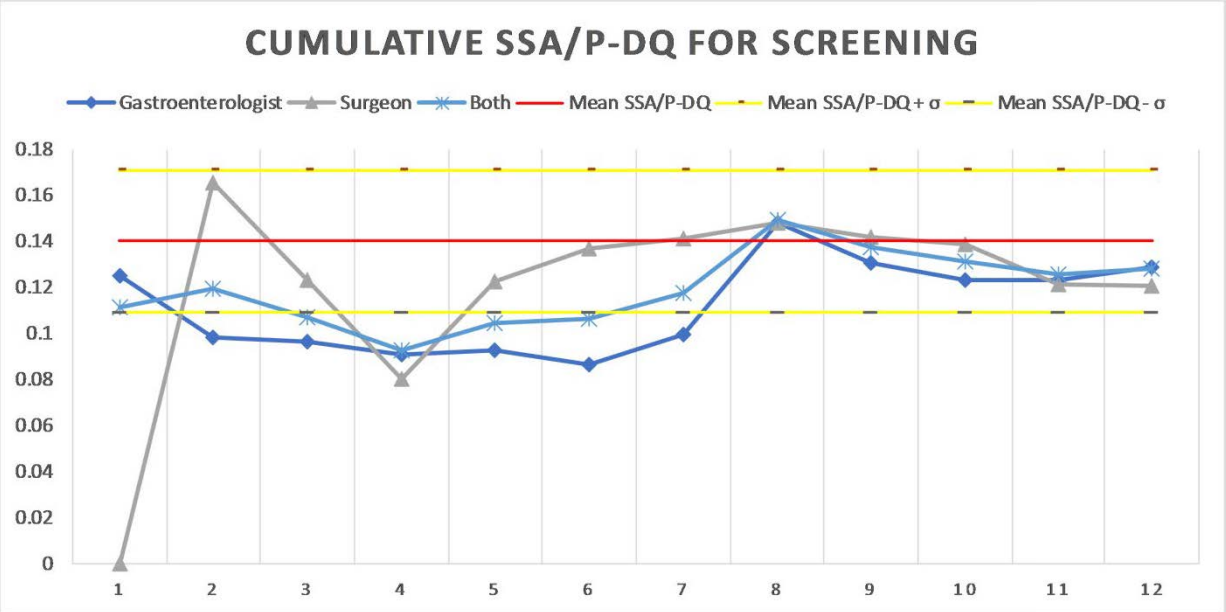
1 AIHW. National Bowel Cancer Screening Program: monitoring report 2018. AIHW; 2018.
2 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394–424.
3 Bettington M, Walker N, Clouston A, Brown I, Leggett B, Whitehall V. The serrated pathway to colorectal carcinoma: current concepts and challenges. Histopathology. 2013 Feb;62(3):367–86.
4 Terada T. Histopathologic study of the rectum in 1,464 consecutive rectal specimens in a single Japanese hospital: II. malignant lesions. Int J Clin Exp Pathol. 2013;6(3):385–94.
5 van Rossum LG, van Rijn AF, Verbeek AL, van Oijen MG, Laheij RJ, Fockens P, et al. Colorectal cancer screening comparing no screening, immunochemical and guaiac fecal occult blood tests: a cost-effectiveness analysis. Int J Cancer. 2011 Apr;128(8):1908–17.
6 He X, Hang D, Wu K, Nayor J, Drew DA, Giovannucci EL, et al. Long-term Risk of Colorectal Cancer After Removal of Conventional Adenomas and Serrated Polyps. Gastroenterology. 2019 Jul;S0016-5085(19)41086-X.
7 Helsingen LM, Vandvik PO, Jodal HC, Agoritsas T, Lytvyn L, Anderson JC, et al. Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a clinical practice guideline. BMJ. 2019 Oct;367:l5515.
8 Lee JK, Jensen CD, Levin TR, Doubeni CA, Zauber AG, Chubak J, et al. Long-term Risk of Colorectal Cancer and Related Death After Adenoma Removal in a Large, Community-based Population. Gastroenterology. 2019, Epub ahead of print.
9 Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med. 2014 Apr;370(14):1298–306.
10 Chittleborough TJ, Kong JC, Guerra GR, Ramsay R, Heriot AG. Colonoscopic surveillance: quality, guidelines and effectiveness. ANZ J Surg. 2018 Jan;88(1-2):32–8.
11 Laird-Fick HS, Chahal G, Olomu A, Gardiner J, Richard J, Dimitrov N. Colonic polyp histopathology and location in a community-based sample of older adults. BMC Gastroenterol. 2016 Aug;16(1):90.
12 Bettington M, Walker N, Rosty C, Brown I, Clouston A, McKeone D, et al. Clinicopathological and molecular features of sessile serrated adenomas with dysplasia or carcinoma. Gut. 2017 Jan;66(1):97–106.
13 Erichsen R, Baron JA, Hamilton-Dutoit SJ, Snover DC, Torlakovic EE, Pedersen L, et al. Increased Risk of Colorectal Cancer Development Among Patients With Serrated Polyps. Gastroenterology. 2016 Apr;150(4):895–902.e5.
14 Melson J, Ma K, Arshad S, Greenspan M, Kaminsky T, Melvani V, et al. Presence of small sessile serrated polyps increases rate of advanced neoplasia upon surveillance compared with isolated low-risk tubular adenomas. Gastrointest Endosc. 2016 Aug;84(2):307–14.
15 Payne SR, Church TR, Wandell M, Rösch T, Osborn N, Snover D, et al. Endoscopic detection of proximal serrated lesions and pathologic identification of sessile serrated adenomas/polyps vary on the basis of center. Clin Gastroenterol Hepatol. 2014 Jul;12(7):1119–26.
16 Lee J, Park SW, Kim YS, Lee KJ, Sung H, Song PH, et al. Risk factors of missed colorectal lesions after colonoscopy. Medicine (Baltimore). 2017 Jul;96(27):e7468.

17 Mandaliya R, Baig K, Barnhill M, Murugesan V, Som A, Mohammed U, et al. Significant Variation in the Detection Rates of Proximal Serrated Polyps Among Academic Gastroenterologists, Community Gastroenterologists, and Colorectal Surgeons in a Single Tertiary Care Center. Dig Dis Sci. 2019 Sep;64(9):2614–21.
18 Francis DL, Rodriguez-Correa DT, Buchner A, Harewood GC, Wallace M. Application of a conversion factor to estimate the adenoma detection rate from the polyp detection rate. Gastrointest Endosc. 2011 Mar;73(3):493–7.
19 Patel NC, Islam RS, Wu Q, Gurudu SR, Ramirez FC, Crowell MD, et al. Measurement of polypectomy rate by using administrative claims data with validation against the adenoma detection rate. Gastrointest Endosc. 2013 Mar;77(3):390–4.
20 Elhanafi S, Ortiz AM, Yarlagadda A, Tsai C, Eloliby M, Mallawaarachchi I, et al. Estimation of the Adenoma Detection Rate From the Polyp Detection Rate by Using a Conversion Factor in a Predominantly Hispanic Population. J Clin Gastroenterol. 2015 Aug;49(7):589–93.
21 Murchie B, Tandon K, Zackria S, Wexner SD, O'Rourke C, Castro FJ. Can polyp detection rate be used prospectively as a marker of adenoma detection rate? Surg Endosc. 2018 Mar;32(3):1141–8.
22 Cicchetti DV. Guidelines, Criteria, and Rules of Thumb for Evaluating Normed and Standardized Assessment Instruments in Psychology. Psychol Assess. 1994;6(4):284–90.
23 Hazewinkel Y, de Wijkerslooth TR, Stoop EM, Bossuyt PM, Biermann K, van de Vijver MJ, et al. Prevalence of serrated polyps and association with synchronous advanced neoplasia in screening colonoscopy. Endoscopy. 2014 Mar;46(3):219–24.
24 Lee CK, Kim YW, Shim JJ, Jang JY. Prevalence of proximal serrated polyps and conventional adenomas in an asymptomatic average-risk screening population. Gut Liver. 2013 Sep;7(5):524–31.
25 Zhu H, Qin H, Huang Z, Li S, Zhu X, He J, et al. Clinical significance of programmed death ligand-1 (PD-L1) in colorectal serrated adenocarcinoma. Int J Clin Exp Pathol. 2015 Aug;8(8):9351–9.
26 Gurudu SR, Heigh RI, De Petris G, Heigh EG, Leighton JA, Pasha SF, et al. Sessile serrated adenomas: demographic, endoscopic and pathological characteristics. World J Gastroenterol. 2010 Jul;16(27):3402–5.
27 Abdeljawad K, Vemulapalli KC, Kahi CJ, Cummings OW, Snover DC, Rex DK. Sessile serrated polyp prevalence determined by a colonoscopist with a high lesion detection rate and an experienced pathologist. Gastrointest Endosc. 2015 Mar;81(3):517–24.
28 IJspeert JE, de Wit K, van der Vlugt M, Bastiaansen BA, Fockens P, Dekker E; JE IJ. Prevalence, distribution and risk of sessile serrated adenomas/polyps at a center with a high adenoma detection rate and experienced pathologists. Endoscopy. 2016 Aug;48(8):740–6.
29 Bettington M, Walker N, Rahman T, Vandeleur A, Whitehall V, Leggett B, et al. High prevalence of sessile serrated adenomas in contemporary outpatient colonoscopy practice. Intern Med J. 2017 Mar;47(3):318–23.
30 Ohki D, Tsuji Y, Shinozaki T, Sakaguchi Y, Minatsuki C, Kinoshita H, et al. Sessile serrated adenoma detection rate is correlated with adenoma detection rate. World J Gastrointest Oncol. 2018 Mar;10(3):82–90.
31 Pyo JH, Ha SY, Hong SN, Chang DK, Son HJ, Kim KM, et al. Identification of risk factors for sessile and traditional serrated adenomas of the colon by using big data analysis. J Gastroenterol Hepatol. 2018 May;33(5):1039–46.
32 Crockett SD, Nagtegaal ID. Terminology, Molecular Features, Epidemiology, and Management of Serrated Colorectal Neoplasia. Gastroenterology. 2019 Oct;157(4):949–966.e4.

5.4 Supplementary material for Chapter 5



Supplementary figure 1 Cumulative ADQ for screening colonoscopies



Supplementary figure 2 Cumulative SSA/P-DQ for screening colonoscopies

Supplementary table 1 – Polyp histology by size threshold

Diminutive (<=5mm) rectosigmoid polyps		
Adenomas	226	(32.3%)
Tubular adenoma	215	(30.7%)
Tubulovillous adenoma	11	(1.6%)
Villous adenoma	0	(0%)
Serrated polyps	424	(60.5%)
Hyperplastic polyp	345	(49.2%)
Sessile serrated adenoma/polyp	77	(11.0%)
Traditional serrated adenoma	2	(0.3%)
Hamartoma	1	(0.1%)
Inflammatory	3	(0.4%)
Leiomyoma	2	(0.3%)
Normal mucosa	45	(6.4%)
Serrated polyps >=10 mm proximal to sigmoid		
Hyperplastic polyp (%)	2	(8.7%)
Sessile serrated adenoma/polyp (%)	21	(91.3%)
Serrated polyps <10 mm proximal to sigmoid		
Hyperplastic polyp (%)	15	(22.73%)
Sessile serrated adenoma/polyp (%)	51	(77.27%)

Supplementary table 2 – Individual results for predicted and actual adenoma and SSA/P detection rates (low numbers group - all indications)

Endoscopist	1	2	3	4	5	6	7	8	9
N	114	86	63	28	54	136	133	162	130
PDR	47.37%	38.37%	76.19%	50.00%	48.15%	48.53%	39.10%	34.57%	38.46%
Predicted ADR	32.21%	26.09%	51.81%	34.00%	32.74%	33.00%	26.59%	23.51%	26.15%
Actual ADR	30.70%	25.58%	38.10%	39.29%	24.07%	20.59%	27.07%	27.16%	34.62%
Actual-predicted ADR gap	-1.51%	-0.51%	-13.71%	5.29%	-8.67%	-12.41%	0.48%	3.65%	8.46%
Predicted SSA/P-DR	6.63%	5.37%	10.67%	7.00%	6.74%	6.79%	5.47%	4.84%	5.38%
Actual SSA/P-DR	5.26%	4.65%	3.17%	0.00%	9.26%	6.62%	4.51%	4.94%	3.08%
Actual-predicted SSA/P-DR gap	-1.37%	-0.72%	-7.49%	-7.00%	2.52%	-0.18%	-0.96%	0.10%	-2.31%

ADR – adenoma detection rate

SSA/P-DR – sessile serrated adenoma/polyp detection rate

PDR – polyp detection rate

Chapter 6

Randomised controlled trial comparing modified Sano's and narrow band imaging international colorectal endoscopic classifications for colorectal lesions

This chapter offers a brief summary of a paper published in the *World Journal of Gastrointestinal Endoscopy*. The statement of authorship and paper (.pdf) 'Randomised controlled trial comparing modified Sano's and narrow band imaging international colorectal endoscopic classifications for colorectal lesions' follow over the page.

6.1 Summary

Several classifications have been used in the past decades in an attempt to predict the histology of colorectal lesions. With advancing technology, virtual chromoendoscopy methods have gradually become the main tools to optimally make predictions during a colonoscopy, and narrow band imaging (NBI) is currently the most available and commonly studied virtual chromoendoscopy method. Many of the endoscopy classifications currently in use are based on this technology.

The modified Sano's (MS) classification, a comprehensive five type classification first described in 2013, appears to be able to accurately discern most types of colorectal lesion with malignant potential. However, before this study, the MS has never been compared to the state-of-the-art available classifications. In this study, we have compared the MS with the most used classification in the West (NICE classification) using a randomised single centre trial focusing on dichotomic outcomes. The first outcome was the differentiation of neoplastic lesions from non-neoplastic lesions, and the second was the identification of resectable lesions (i.e. not benign and not invasive).

In this trial, 348 patients had their 647 colorectal lesions evaluated using either classification. The area under the receiver operating characteristic curve (AUC) for differentiating neoplastic from non-neoplastic lesions was 0.92 for the MS and 0.78 for NICE. For predicting 'endoscopic resectability', the AUC was 0.92 for the MS and 0.83 for NICE. Both the AUC values reached statistical significance. The post-polypectomy surveillance interval was accurately determined by the MS in 98.2% of patients and in 92.1% of patients for NICE. In addition, the accuracy for diagnosis of sessile serrated adenoma/polyp (SSA/P) with high confidence utilizing the MS classification achieved 93.2%.

Although in this study we were unable to compare directly the capabilities of both classifications in differentiating serrated lesions, our research was able to demonstrate the potential of the MS as a more accurate method of classification than the one currently in use in the West.

6.2 Statement of authorship

Statement of Authorship

Title of Paper	Randomised controlled trial comparing modified Sano's and narrow band imaging international colorectal endoscopic classifications for colorectal lesions.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Randomised controlled trial comparing modified Sano's and narrow band imaging international colorectal endoscopic classifications for colorectal lesions. Pu LZCT, Cheong KL, Koay DSC, Yeap SP, Ovenden A, Raju M, Ruszkiewicz A, Chiu PW, Lau JY, Singh R. World J Gastrointest Endosc. 2018 Sep 16;10(9):210-218. doi:10.4253/wjge.v10.i9.210. PubMed PMID: 30283604

Principal Author

Name of Principal Author (Candidate)	Leonardo Zorron Cheng Tao Pu		
Contribution to the Paper	Involved in data processing and statistical analysis. Interpreted the results and prepared the manuscript.		
Overall percentage (%)	60%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	23/03/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate to include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Name of Co-Author	Andrew Ruszkiewicz		
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Name of Co-Author	James Y Lau		
Contribution to the Paper	Involved in the design of the study. Contributed with critical revision of the article for important intellectual content. Contributed with patient data to the study.		
Signature		Date	15/4/2019

Name of Co-Author	Rajvinder Singh		
Contribution to the Paper	Involved in the conceptualisation and designed of the study. Supervised the collection of data. Contributed with critical revision of the article for important intellectual content.		
Signature		Date	21/3/09

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ORIGINAL ARTICLE

Randomized Controlled Trial

Randomised controlled trial comparing modified Sano's and narrow band imaging international colorectal endoscopic classifications for colorectal lesions

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Author contributions: Zorrón Cheng Tao Pu L organized and analysed the raw soft copy data, created tables and figures and drafted the final version of the manuscript; Cheong KL, Koay DSC and Yeap SP collected the raw hard copy data, and provided interim analysis and drafts; Ovenden A contributed with the conversion of data from hard copy to soft copy and with the logistics for data collection and storage; Raju M assisted with editing and proofreading of the final manuscript; Ruszkiewicz A contributed with specialized Pathology input from the design to the final manuscript; Chiu PW, Lau JY and Singh R designed and coordinated the study. Singh R performed all colonoscopies in this study; All authors reviewed and approved the final manuscript.

Institutional review board statement: This study was approved by the Australian Human Research Ethics Committee (TQEH/LMH/MH).

Clinical trial registration statement: This study is registered at http://clinicaltrials.gov. The registration identification number is NCT02963207.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrolment.

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Abstract

AIM

To assess the utility of modified Sano's (MS) *vs* the

narrow band imaging international colorectal endoscopic (NICE) classification in differentiating colorectal polyps.

METHODS

Patients undergoing colonoscopy between 2013 and 2015 were enrolled in this trial. Based on the MS or the NICE classifications, patients were randomised for real-time endoscopic diagnosis. This was followed by biopsies, endoscopic or surgical resection. The endoscopic diagnosis was then compared to the final (blinded) histopathology. The primary endpoint was the sensitivity (Sn), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of differentiating neoplastic and non-neoplastic polyps (MS Ⅱ/Ⅱo/Ⅲa/Ⅲb *vs* I or NICE 1 *vs* 2/3). The secondary endpoints were "endoscopic resectability" (MS Ⅱ/Ⅱo/Ⅲa *vs* Ⅰ/Ⅲb or NICE 2 *vs* 1/3), NPV for diminutive distal adenomas and prediction of post-polypectomy surveillance intervals.

RESULTS

A total of 348 patients were evaluated. The Sn, Sp, PPV and NPV in differentiating neoplastic polyps from non-neoplastic polyps were, 98.9%, 85.7%, 98.2% and 90.9% for MS; and 99.1%, 57.7%, 95.4% and 88.2% for NICE, respectively. The area under the receiver operating characteristic curve (AUC) for MS was 0.92 (95%CI: 0.86-0.98); and AUC for NICE was 0.78 (95%CI: 0.69, 0.88). The Sn, Sp, PPV and NPV in predicting "endoscopic resectability" were 98.9%, 86.1%, 97.8% and 92.5% for MS; and 98.6%, 66.7%, 94.7% and 88.9% for NICE, respectively. The AUC for MS was 0.92 (95%CI: 0.87-0.98); and the AUC for NICE was 0.83 (95%CI: 0.75-0.90). The AUC values were statistically different for both comparisons (P = 0.0165 and P = 0.0420, respectively). The accuracy for diagnosis of sessile serrated adenoma/polyp (SSA/P) with high confidence utilizing MS classification was 93.2%. The differentiation of SSA/P from other lesions achieved Sp, Sn, PPV and NPV of 87.2%, 91.5%, 89.6% and 98.6%, respectively. The NPV for predicting adenomas in diminutive rectosigmoid polyps (n = 150) was 96.6% and 95% with MS and NICE respectively. The calculated accuracy of post-polypectomy surveillance for MS group was 98.2% (167 out of 170) and for NICE group was 92.1% (139 out of 151).

CONCLUSION

The MS classification outperformed the NICE classification in differentiating neoplastic polyps and predicting endoscopic resectability. Both classifications met ASGE PIVI thresholds.

Key words: Colorectal polyps; Colorectal adenomas; Colorectal neoplasm; Colorectal lesions; Randomised controlled trial; Colonoscopy; Magnifying colonoscopy; Endoscopic imaging

Core tip: Endoscopic differentiation of colorectal polyps can be daunting. Especially with serrated lesions. The Modified Sano's (MS) classification, the first classification that included sessile serrated adenoma/polyps was developed in 2013. In this randomised controlled trial we compare the accuracies of the well-established narrow band imaging international colorectal endoscopic classification and the MS classification. Although both classifications have met the ASGE PIVI statement thresholds for predicting histology in diminutive rectosigmoid polyps and post-polypectomy surveillance, MS was statistically more accurate.

Zorrón Cheng Tao Pu L, Cheong KL, Koay DSC, Yeap SP, Ovenden A, Raju M, Ruszkiewicz A, Chiu PW, Lau JY, Singh R. Randomised controlled trial comparing modified Sano's and narrow band imaging international colorectal endoscopic classifications for colorectal lesions. *World J Gastrointest Endosc* 2018; 10(9): 210-218 Available from: URL: http://www.wjgnet.com/1948-5190/full/v10/i9/210.htm DOI: http://dx.doi.org/10.4253/wjge.v10.i9.210

INTRODUCTION

The majority of colorectal polyps are small and benign[1]. Current practice mandates biopsies or removal and pathological interpretation to confirm the diagnosis. With technological advancement in the endoscopy imaging field, the adoption of strategies such as "diagnose, resect and discard" for proximal polyps and "do not resect" for rectosigmoid hyperplastic polyps (HPs) has become possible[2,3]. Apart from being cost-effective and perhaps time-efficient, these strategies could potentially reduce the risks of complications associated with polypectomy[4]. For larger lesions, advanced imaging modalities may have a role especially if required to differentiate early cancers confined to the intramucosal layer or infiltrating more than 1000 μm into the submucosa[5-8]. *In vivo* prediction of colorectal lesions is hence of utmost importance.

Numerous technologies including iScan, flexible spectral imaging colour enhancement (FICE) and narrow band imaging (NBI) have been available to assist in interrogating the surface pattern and microvascular architecture of colorectal polyps. A systematic review comparing standard white light endoscopy, chromoendoscopy and NBI with or without magnification concluded that magnified chromoendoscopy and NBI were the two most accurate modalities in predicting polyp histology[9]. Several studies have demonstrated that NBI is equivalent to chromoendoscopy in distinguishing neoplastic and non-neoplastic colonic polyps. A recent meta-analysis involving 28 studies reported high accuracy with NBI in diagnosing colorectal polyps based on an area under the hierarchical summary receiver-operating characteristic (HSROC) curve of 0.92[10]. Additionally, when high confidence predictions are made, the sensitivity (Sn) and negative predictive value (NPV) exceeded 90%. Sessile serrated adenoma/polyp (SSA/P) was not considered

Table 1 Narrow band imaging international colorectal endoscopic classification of colorectal polyps was based on 3 features including colour, vessel, architecture and surface pattern

	NICE Ⅰ	NICE Ⅱ	NICE Ⅲ
Colour	Same or lighter than background	Browner than background	Dark brown relative to background +/- patchy whiter areas
Vessels	None or isolated lacy vessels	Brown vessels surrounding white structures	Disrupted or missing vessels
Surface pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structure surrounded by brown vessels	Amorphous or absent surface pattern
Likely pathology	Hyperplastic	Adenoma	Deep submucosal invasive cancer

NICE: Narrow band imaging international colorectal endoscopic.

separately in these studies[10-13].

Differentiation of polyps can also be made using NBI with magnified endoscopy (NBI-ME) utilizing various classifications including the Sano's classification, modified Sano's (MS) classification, NBI international colorectal endoscopic (NICE), Hiroshima, Showa, Workgroup serrAted Polyps and Polyposis (WASP), JNET and Jikei classifications and 1 published classification for FICE with magnified endoscopy (FICE-ME)[5,11,14-17]. Many of these classifications have been validated in various studies. There are however no comparative data to date on the diagnostic accuracy of these different classifications. Recently the new WASP classification has emerged which included the differentiation of SSA/Ps from HP, but with inconsistent results[18]. The Sano's classification was modified to include a classification for SSA/P in 2013[19]. As the original Sano's classification was solely based on capillary pattern, the surface pattern was incorporated in the MS classification, in order to improve its diagnostic capability. The MS classification is defined in accordance with the colour, capillary network surrounding the pit pattern and surface pattern evaluated under magnification. By contrast, the NICE classification of colorectal polyps is based on 3 features including colour, vessel architecture and surface pattern evaluated not necessarily under magnification (Figure 1 and Table 1, respectively). Both the NICE and MS have been found to be independently valid tools for predicting polyp histology according to the American Society for Gastrointestinal Endoscopy (ASGE) Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) statement[5,6,19,20].

The ASGE's PIVI statement[20] regarding colonic polyps has advised thresholds for endoscopic imaging, namely: (1) an endoscopic technology (when used with high confidence) should provide > 90% agreement in determining post-polypectomy surveillance intervals; and (2) the technology (when used with high confidence) should provide > 90% NPV for adenomatous histology for rectosigmoid polyps.

This was introduced to further guide endoscopists using new technologies into achieving measurable outcomes and aiding the incorporation of novel technologies into clinical practice.

There are no randomised trials comparing MS and NICE classifications. The aim of this study is to compare the accuracy of NBI with dual focus (DF) magnification in differentiating colorectal polyps using the NICE and the MS classifications. The NPV for neoplastic prediction (cancer, adenomas and SSA/Ps) within diminutive rectosigmoid polyps and the post-polypectomy surveillance intervals for each classification (based on the ASGE PIVI statement thresholds) was also evaluated.

MATERIALS AND METHODS

Study design

This study was approved by the Australian Human Research Ethics Committee (TQEH/LMH/MH) and is registered on clinicaltrials.gov (No. NCT02963207). Written informed consent was obtained from each patient prior to colonoscopy. Data were collected at the site of investigation by a research nurse and analysed by a study statistician. Only the endoscopist knew which arm of the trial the patient was on during the endoscopic diagnosis of the lesion. Neither the patient nor the pathologist was aware of the classification used on the lesion.

Randomisation

A concealed container containing 2 cards which randomised the participants to either MS or NICE classifications arm was used. Each week, a research nurse randomly selected a card from the concealed container. This generated allocation was then conveyed to the endoscopist.

Study population

All patients undergoing colonoscopy for any indication at the Lyell McEwin Hospital endoscopy unit were evaluated for eligibility by the researchers. Patients were recruited from June 2013 onwards. Inclusion criteria were age of 18 years or older with endoscopic findings of colonic polyps (of any size). Key exclusion criteria included known history of inflammatory bowel disease, familial polyposis syndrome, coagulopathy, thrombocytopenia, incomplete procedure due to poor bowel preparation or acute angles, current pregnancy and no polyps detected during the procedure.

All colonoscopies were performed by a senior endoscopist with a high level of expertise using the 190 series with DF capability (Exera Ⅲ NBI system; Olympus Co. Ltd, Japan). This processor allows the NBI image to be enhanced by 150%. The DF function enables

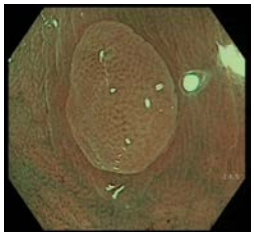
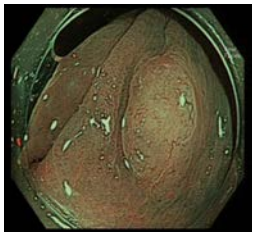
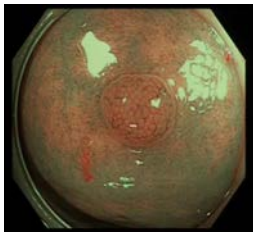
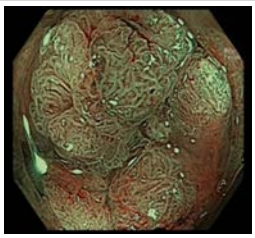
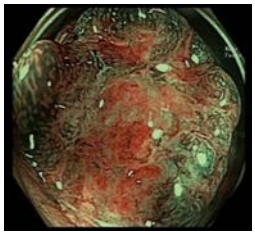
MS classification (predicted histology)	Description	Example
Category Ⅰ (HP)	Pale colour ± round pits with central brown star-like dots or bland appearance ± minute capillaries that may meander across polyp	
Category Ⅱo (SSA/P)	Pale or light dark colour ± open pits ± 3 out of 5: cloud-like surface, inconspicuous margins, mucous cap, irregular shape and varicose microvascular vessels[1]	
Category Ⅱ (tubular adenoma with low grade dysplasia)	Light dark or dark colour ± white linear or oval pits ± linear or oval regular capillary network surrounding pits	
Category Ⅲa (high grade dysplasia/ villous or tubulovillous adenoma/superficial cancer)	Light dark or dark colour ± white villous/cerebriform pits ± tortuous/branched mildly regular capillary network surrounding pits[2]	
Category Ⅲb (invasive cancer)	Dark surroundings with pale central area ± loss of pits and vascular pattern	

Figure 1 Modified Sano's classification is defined as below. [1]If no open pits and 2 serrated features = classified as low confidence for SSA/P; if 1 serrated feature = low confidence for HP; if no features = high confidence for HP. [2]Can have slight loss of pit pattern and vascularity when leaning towards superficial cancer.MS: Modified Sano's; HP: hyperplastic polyp; SSA/P: Sessile serrated adenoma/polyp.

magnification of up to 70×. Both are push button techniques and image enhancement with magnification occurs within 1-2 s.

Endoscopic imaging and classification of polyps

The patients whom had colonic polyps had their polyps assessed in real-time with NBI-DF. DF was used in both groups to standardize the evaluation. The endoscopist studied the lesion carefully at least for one minute. The size of the polyp was estimated by the endoscopist based on the size of the cap (outer diameter of 15 mm) and/or size of the snare/forceps. The polyp was initially examined in white light, then NBI, followed by magnification. Image acquisition was further enhanced with a distal cap attachment to the scope (short transparent cap from Olympus® - D-201, approximately 4 mm from distal end). Efforts were made to obtain a crisp clear still image with water pump and simeticone when needed (no dyes used). Histology in real-time of individual polyps was then predicted using either the NICE or the MS classification, with a confidence level (low/high).

The endoscopist scored each polyp found and the final endoscopic diagnosis was recorded by the research nurse who was present in the endoscopy suite. A clinical judgement was deemed as high in confidence when the endoscopist found a polyp with clear features of one subtype, as described in the classifications shown in Figure 1 and Table 1. If there was any uncertainty or doubt, the prediction was recorded as low confidence.

Table 2 Demographics of study participants

Classification	Modified Sano's	NICE	*P* value
age (mean ± SD)	62.18 ± 14.06	64.41 ± 11.36	NS
M:F (% male)	191:118 (62%)	178:76 (70%)	NS
Indication *n* (%)			
Screening	156 (50)	115 (45)	NS
Surveillance	86 (28)	88 (35)	
Symptoms	63 (20)	49 (19)	
Others	4 (1)	2 (1)	
Total	309	254	

NICE: Narrow band imaging international colorectal endoscopic; NS: Non-significant.

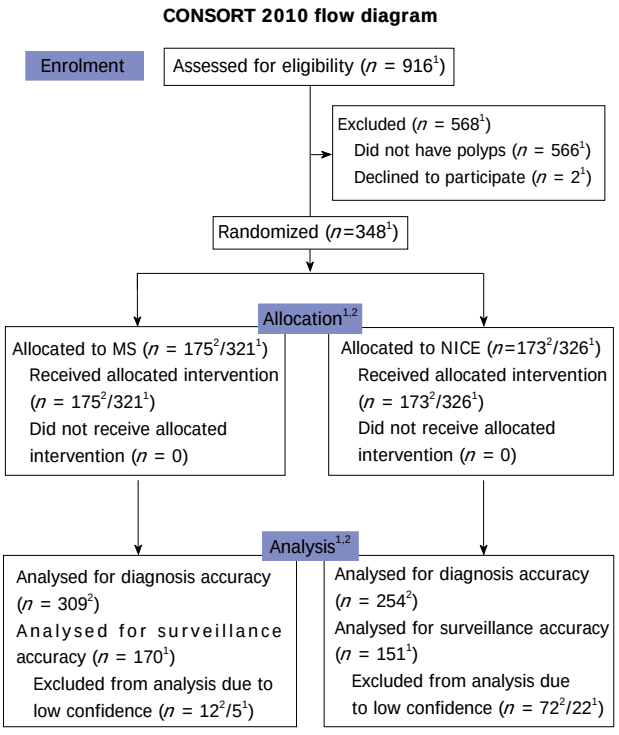


Figure 2 CONSORT 2010 flow diagram. [1]Patients; [2]Polyps. MS: Modified Sano's; NICE: Narrow band imaging international colorectal endoscopic; SSA/P: Sessile serrated adenoma/polyp.

All polyps were photographed and stored for future reference. No video recording was done. This was followed by biopsies and surgical resection in cases of predicted invasive cancer, or endoscopic resection to the remaining lesions. The histopathology was evaluated initially by a non-gastrointestinal (non-GI) specialist pathologist due to personnel limitations. However, if the diagnosis was uncertain the slides were forwarded to a specialist GI pathologist. The pathologists were blinded to the classification used and the prediction of the polyp by the endoscopist. The endoscopy diagnosies was then compared to the final histopathological diagnosis.

Study endpoints

The primary endpoint of the study was to prospectively evaluate the Sn, specificity (Sp), positive predictive value (PPV) and NPV of neoplastic (cancer, adenoma or SSA/P) *vs* non-neoplastic (HP, inflammatory) polyps based on either classification (MS Ⅱ, Ⅱo, Ⅲa and Ⅲb *vs* MS Ⅰ or NICE 2, 3 *vs* NICE 1).

In addition, we assessed the concept of "suitability of endoscopic resection" of these polyps (MS Ⅱ, Ⅱo, Ⅲa *vs* MS Ⅰ, Ⅲb or NICE 2 *vs* NICE 1, 3) and the diagnostic accuracy of SSA/Ps by the MS classification. To assess the ability of the NICE and MS classifications to match the PIVI-1 thresholds, high confidence NBI predictions of polyp histology were given an endoscopy-based surveillance interval. This was then compared with the recommended interval based on histologic assessment. For this calculation, polyps histologically classified as SSA/Ps but classified as NICE 1 or MS Ⅰ were excluded. This was thought to mitigate bias as NICE has no separate SSA/P classification. As for the PIVI-2 thresholds, we calculated the negative predictive value (NPV) of high confidence NBI predictions for adenomatous histology of diminutive polyps using histology as a reference.

Statistical analysis

The sample size was calculated based on number of polyps. The primary aim was to test the performance of NBI diagnosis for polyp differentiation. Thus, it was estimated that a total sample size of 560 polyps would be required to have an 80% power with an alpha error of 0.05 to appreciate an increment of 7% in the prediction of histology with the MS classification.

Statistical analysis was performed by using statistical software, Stata 13.0 (StatCorp, TX, United States). Continuous variables are reported as either a mean ± SD or median and range. Means were reported unless the data were nonparametric. The Student's *t* test was used to analyse continuous variables, and a Pearson χ^2 analysis was used for categorical variables. Statistical significance was set at a 2-sided *P* value of 0.05 or less. The analysis applied to the classifications was in regards to the polyps, while the analysis for post-polypectomy surveillance was based on patients.

RESULTS

A total of 348 patients were included from June 2013 until June 2015 (Figure 2). The trial was terminated as we have reached the stipulated sample size. Both groups had similar demographics (Table 2). The total number of polyps predicted with high confidence in the MS classification was 309 out of 321 (96.3%). This was significantly higher in proportion as compared to that in the NICE arm (254 out of 326 polyps or 78% - as shown in Table 3). Characteristics of the polyps were not significantly different between both arms except for the mean size of polyps which was larger for the NICE arm (Table 3).

Primary endpoint

The Sn, Sp, PPV and NPV in differentiating neoplastic from non-neoplastic polyps were 98.9%, 85.7%, 98.2%

Table 3 Characteristics of colon polyps

Classification	Modified Sano's	NICE	*P* value
Confidence level *n* (%)			
High	309 (96.3)	254 (78)	<0.0001
Low	12 (3.7)	72 (22)	
Total	321	326	
Distribution based on size			
⩽ 5 mm	151	127	NS
6-9 mm	63	42	
⩾ 10 mm	95	85	
Size (mean ± SD, mm)	10.17 ± 11.30	14.48 ± 19.47	0.0036
Polyp distribution *n* (%)			
Right colon	95 (31)	101 (40)	NS
Transverse colon	60 (19)	52 (20)	
Descending colon	34 (11)	27 (11)	
Rectosigmoid colon	120 (39)	74 (29)	
Total	309	254	
Paris *n* (%)			
1p	28 (9)	18 (7)	NS
1s	190 (61)	156 (61)	
2a	81 (26)	71 (28)	
2b	4 (1)	1 (1)	
2c	5 (2)	6 (2)	
3	1 (1)	2 (1)	
Others	12	15	
Total	309	254	

NICE: Narrow band imaging international colorectal endoscopic; NS: Non-significant.

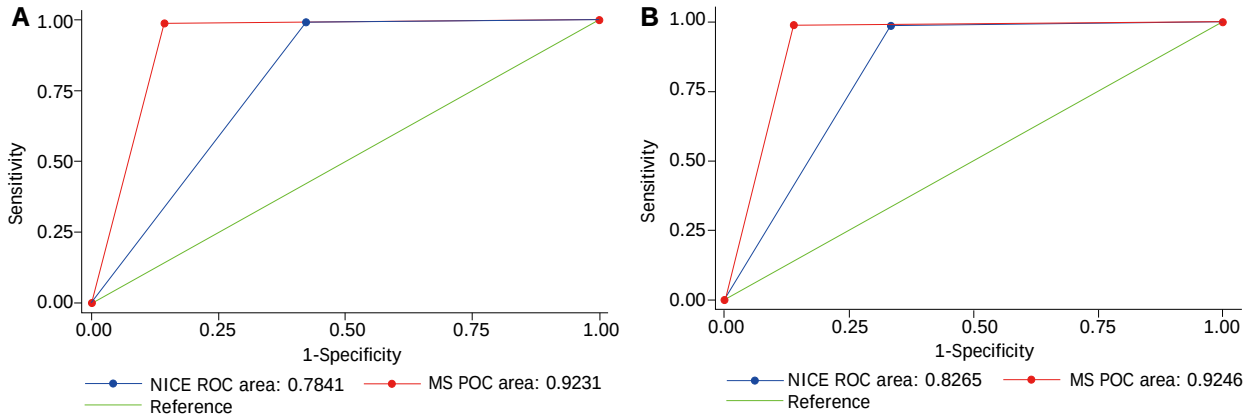


Figure 3 Receiver operating characteristic curves of modified Sano's and narrow band imaging international colorectal endoscopic classification. A: For neoplastic differentiation; B: For endoscopic resectability. MS: Modified Sano's; NICE: Narrow band imaging international colorectal endoscopic; SSA/P: Sessile serrated adenoma/polyp.

and 90.9% for MS and 99.1%, 57.7%, 95.4% and 88.2% for NICE respectively. The MS arm had an area under the receiver operating characteristic curve (AUC) of 0.92 (95%CI: 0.86-0.98), whilst NICE had an AUC of 0.78 (95%CI: 0.69-0.88). There was a statistically significant difference between the MS and NICE's AUC values (P = 0.0165) (Figure 3A).

Secondary endpoints

The Sn, Sp, PPV and NPV in predicting 'endoscopic resectability' were 98.9%, 86.1%, 97.8% and 92.5% for MS and 98.6%, 66.7%, 94.7% and 88.9% for NICE respectively. The MS group had an AUC of 0.92 (95%CI: 0.87-0.98), whereas NICE had an AUC of 0.83 (95%CI: 0.75, 0.90). There was also a statistically significant difference between the AUC values (P = 0.0420) (Figure 3B).

The accuracy for diagnosis of SSA/P with high confidence using Ⅱo on MS classification was 93.2%, and differentiation of SSA/P from other lesions achieved 87.2% of Sp, 91.5% of Sn, 89.6% of PPV and 98.6% of NPV (Table 4).

Classification of polyps according to size is shown in Table 3. Of the high confidence polyps in the MS arm, 150 (48.5%) were diminutive (5 mm or less), 60 (19.5%) were small (6-9 mm) and 99 (32%) were large (⩾ 10 mm). In the NICE arm, there were 254 polyps detected with high confidence which included 127 (50%) diminutive, 42 (16.5%) small and 85 (33.5%) large polyps.

The NPV for diminutive rectosigmoid polyps were 96.6% and 95% in MS and NICE arms respectively. The

Table 4 Accuracy of modified sano's Ⅱo class for sessile serrated adenoma/polyp

	SSA/P	Other histology
MS Ⅱo	43 (13)	5 (1.54)
Other MS classification	4 (1.23)[1]	273 (84)

[1]SSA/P histology was correlated with either Ⅰ or Ⅱo on MS. SSA/P: Sessile serrated adenoma/polyp; MS: Modified Sano's.

Table 5 Results of *in vivo* prediction for post-polypectomy surveillance interval

	Modified Sano's	NICE
Total patients	175	173
Accurate	167	139
Overcalled[1]	2	8
Undercalled[2]	1	4
Excluded	5	22

[1]Surveillance colonoscopy interval prediction with classification was premature compared to the determined by final histology; [2]Surveillance colonoscopy interval prediction with classification was delayed compared to the determined by final histology. NICE: Narrow band imaging international colorectal endoscopic.

calculated accuracy of post-polypectomy surveillance for MS group was 98.2% (167 out of 170) and for NICE group was 92.1% (139 out of 151).

In the MS arm, there were 20 out 309 (6.4%) high confidence polyps' inaccuracies. Misdiagnoses which were made were as follows: MS Ⅰ (3 SSA's and 1 normal mucosa), MS Ⅱ (3 normal mucosa, 1 inflammatory polyp, 1 traditional serrated adenoma, 4 tubular adenoma with high grade dysplasia, 1 tubulovillous adenoma with low grade dysplasia and 1 villous adenoma with high grade dysplasia), MS Ⅱo (2 tubular adenoma with low grade dysplasia and 1 HP) and MS Ⅲa (1 tubular adenoma with low grade dysplasia and 1 villous adenoma with invasive carcinoma).

In the NICE arm, there were 18 out of 254 (7.1%) inaccuracies in high confidence polyps - NICE Ⅰ (1 normal mucosa, 2 tubular adenomas with low grade dysplasia), NICE Ⅱ (5 normal mucosa, 5 HPs, 1 inflammatory polyp, 1 focal colitis cystica profunda, 1 cancer) and NICE Ⅲ (1 tubulovillous adenoma with high grade dysplasia).

These resulted in 10 overcalled and 5 undercalled cases on the *in vivo* prediction for post-polypectomy surveillance interval (Table 5).

DISCUSSION

NBI is one of the most easily available and commonly used image-enhanced endoscopic modality. There are many NBI classifications for colorectal lesions, but only two thus far have included SSA/P separately (WASP and MS). The WASP classification was derived from NICE aiming to differentiate HP from SSA/P[18]. The classification does not address the differentiation of adenoma and invasive cancer. A simple, comprehensive and reliable classification is pivotal in clinical practice.

Hewett *et al*[4] has initially shown NICE subtypes 1 and 2 using non-magnified NBI. The accuracy, Sn and NPV for small colorectal polyps were 89%, 98% and 95%, respectively. The study did not include SSA/Ps. In this study, the MS classification has been proven to be more effective in differentiating neoplastic colorectal polyps (*i.e.*, cancer or adenoma or SSA/P) from non-neoplastic polyps (*i.e.*, inflammatory or HP) when compared to the NICE classification. This is probably attributed to the former's design which has a sub-division for SSA/Ps. This subdivision may have given the MS classification an upper-hand over the NICE classification as some of the HP misdiagnosed by the NICE were in fact SSA/Ps.

In this study, both NBI classifications were able to meet the PIVI benchmarks as the post-polypectomy surveillance prediction accuracy and NPV for diminutive rectosigmoid polyps exceeded 90% in the two study arms. These findings are compatible with the results of the previous meta-analysis of 20 studies on NBI with and without magnification. The pooled NPV found was 91% for adenomatous histology[21].

SSA/Ps have been recognized as precancerous lesions and they account for up to one third of all sporadic colorectal cancers[22]. They may have been misdiagnosed due to the challenges both endoscopists and pathologists faced in distinguishing them from HPs for the past years.

Several investigators sought to discriminate SSA/Ps from HPs *via* NBI (without magnification) based on several specific endoscopic features with varying results[23-26]. A recently published prospective study by Yamashina *et al*[27] reported very high sensitivity (98%) but only modest Sp 59.5% for diagnostic criteria of SSA/Ps through identification of "expanded crypt openings" and "thick branched vessels" on magnified NBI. The WASP classification was not used for comparison in this study as it was only recently published and not available when our study began[18]. Similarly, although the JNET is currently being considered a gold standard in regard to polyp classification (excluding SSA/Ps), this had not been published by the time the study started.

The clinical use of real-time histology is already used in standard practice to evaluate "suitability for resection". This means that if a lesion is endoscopically considered to be an invasive cancer or if it is predicted to be benign (*e.g.*, distal diminutive HPs), endoscopic resection will not be attempted. Moreover, further benefits of endoscopic diagnosis may add to this "suitability for resection". Two cost-analysis studies have proven the "diagnose, resect and discard" technique is cost-effective for diminutive polyps[28,29]. There are nevertheless several issues for consideration. For this technique to be adopted globally there should be a standard NBI classification that is easy for inexperienced endoscopists to learn and apply. There is potential risk for litigation if the endoscopists' histology prediction is inaccurate and with a possibility of patients developing advanced pathology during the inter-surveillance period. In addition, the risk of bleeding

and perforation associated with polypectomy may be increased if the endoscopist 'overcalled' any lesion. The MS classification could step in to allow these techniques with the more accurate up-to-date endoscopic diagnosis classification.

This study has limitations. All procedures were performed by a single expert. This may not be generalizable. Although other studies within our centre have validated the usefulness of the MS classification compared to NICE and JNET[30], studies utilizing the MS classification must be performed in other endoscopy centres by experts and non-experts to evaluate its reproducibility. The group randomization process used (per week instead of per patient) was not conventional and could have contributed to uneven distribution among both arms. However, this was not translated in demographic differences (Table 2). The reason for doing so was to mitigate possible confusion on which classification should be used for each patient and in order to allow a consistent mental focus on one classification at a time.

In conclusion, this study demonstrated that the MS classification was superior in differentiating non-neoplastic from neoplastic polyps and more accurately guided the endoscopic resection when compared to the NICE classification. MS is also accurate for predicting SSA/P histology, a subtype neglected by NICE. Nevertheless, both classifications met PIVI thresholds in managing diminutive polyps and determining post-polypectomy surveillance period.

ARTICLE HIGHLIGHTS

Research background

Prediction of polyp histology may prevent unnecessary polypectomies and reduce cost.

Research motivation

The endoscopic differentiation of benign and malignant polyps is sometimes difficult, especially when looking into serrated lesions. Very few endoscopic classifications include the differentiation of sessile serrated lesions [*e.g.*, modified Sano's (MS)]. These have not being widely used partially due to lack of reliable comparison with the currently used classifications [*e.g.*, narrow band imaging international colorectal endoscopic (NICE)]. The comparison of established classifications with a classification including serrated polyps' differentiation in a randomised trial could help to support the use of the newer and more comprehensive classifications.

Research objectives

The main objective of this randomised controlled trial is to compare the established adenoma *vs* non-adenoma NICE classification and the newer neoplastic *vs* non-neoplastic MS classification.

Research methods

This was a single centre randomised controlled trial (pathologist blinded) comparing the NICE classification with the MS classification for the endoscopic prediction of histology of colorectal lesions during colonoscopy.

Research results

MS classification had significantly higher proportion of high confidence diagnoses compared to NICE. Overall, the MS area under the receiver operating characteristic curve (AUC) was 0.92 and NICE AUC was 0.78 (P = 0.0165). For predicting "endoscopic resectability", MS AUC was also 0.92 and NICE AUC was 0.83 (P = 0.0420). The accuracy for diagnosis of SSA/P by MS classification was 93.2%. The NPV for diminutive rectosigmoid polyps were 96.6% and 95% in MS and NICE arms respectively. The calculated accuracy of post-polypectomy surveillance was 98.2% for MS and 92.1% for NICE. Utilizing MS, 6.4% of high confidence polyps were misdiagnosed. Utilizing NICE, 7.1% were misdiagnosed.

Research conclusions

The MS classification has shown to be accurate in diagnosing colorectal lesions including sessile serrated adenoma/polyp. Both classifications surpassed the ASGE PIVI thresholds. MS classification may currently be the most accurate and comprehensive endoscopic classification for differentiation of colorectal polyps.

Research perspectives

The use of classifications that incorporate the differentiation of serrated polyps such as the MS classification may be necessary. These should become the standard for adequate characterization of colorectal lesions. Nonetheless validation in different centres is required.

REFERENCES

1 **Bond JH**. Polyp guideline: diagnosis, treatment, and surveillance for patients with colorectal polyps. Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 2000; **95**: 3053-3063 [PMID: 11095318 DOI: 10.1111/j.1572-0241.2000.03434.x]

2 **Rastogi A**, Rao DS, Gupta N, Grisolano SW, Buckles DC, Sidorenko E, Bonino J, Matsuda T, Dekker E, Kaltenbach T, Singh R, Wani S, Sharma P, Olyaee MS, Bansal A, East JE. Impact of a computer-based teaching module on characterization of diminutive colon polyps by using narrow-band imaging by non-experts in academic and community practice: a video-based study. *Gastrointest Endosc* 2014; **79**: 390-398 [PMID: 24021492 DOI: 10.1016/j.gie.2013.07.032]

3 **Ladabaum U**, Fioritto A, Mitani A, Desai M, Kim JP, Rex DK, Imperiale T, Gunaratnam N. Real-time optical biopsy of colon polyps with narrow band imaging in community practice does not yet meet key thresholds for clinical decisions. *Gastroenterology* 2013; **144**: 81-91 [PMID: 23041328 DOI: 10.1053/j.gastro.2012.09.054]

4 **Hewett DG**, Kaltenbach T, Sano Y, Tanaka S, Saunders BP, Ponchon T, Soetikno R, Rex DK. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. *Gastroenterology* 2012; **143**: 599-607.e1 [PMID: 22609383 DOI: 10.1053/j.gastro.2012.05.006]

5 **Ikematsu H**, Matsuda T, Emura F, Saito Y, Uraoka T, Fu KI, Kaneko K, Ochiai A, Fujimori T, Sano Y. Efficacy of capillary pattern type IIIA/IIIB by magnifying narrow band imaging for estimating depth of invasion of early colorectal neoplasms. *BMC Gastroenterol* 2010; **10**: 33 [PMID: 20346170 DOI: 10.1186/1471-230X-10-33]

6 **Hayashi N**, Tanaka S, Hewett DG, Kaltenbach TR, Sano Y, Ponchon T, Saunders BP, Rex DK, Soetikno RM. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. *Gastrointest Endosc* 2013; **78**: 625-632 [PMID: 23910062 DOI: 10.1016/j.gie.2013.04.185]

7 **Nakadoi K**, Tanaka S, Kanao H, Terasaki M, Takata S, Oka S, Yoshida S, Arihiro K, Chayama K. Management of T1 colorectal carcinoma with special reference to criteria for curative endoscopic resection. *J Gastroenterol Hepatol* 2012; **27**: 1057-1062 [PMID: 22142484 DOI: 10.1111/j.1440-1746.2011.07041.x]

8 **Kitajima K,** Fujimori T, Fujii S, Takeda J, Ohkura Y, Kawamata H, Kumamoto T, Ishiguro S, Kato Y, Shimoda T, Iwashita A, Ajioka Y, Watanabe H, Watanabe T, Muto T, Nagasako K. Correlations

between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. *J Gastroenterol* 2004; **39**: 534–543 [PMID: 15235870 DOI: 10.1007/s00535-004-1339-4]

9 **Subramaniam V,** Mannath J, Hawkey CJ, Ragunath K. Utility of Kudo Pit Pattern for Distinguishing Adenomatous from Non Adenomatous Colonic Lesions In Vivo: Meta-Analysis of Different Endoscopic Techniques. *Gastrointest Endosc* 2009; **69**: AB277 [DOI: 10.1016/j.gie.2009.03.742]

10 **McGill SK**, Evangelou E, Ioannidis JP, Soetikno RM, Kaltenbach T. Narrow band imaging to differentiate neoplastic and non-neoplastic colorectal polyps in real time: a meta-analysis of diagnostic operating characteristics. *Gut* 2013; **62**: 1704-1713 [PMID: 23300139 DOI: 10.1136/gutjnl-2012-303965]

11 **Chiu HM**, Chang CY, Chen CC, Lee YC, Wu MS, Lin JT, Shun CT, Wang HP. A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia. *Gut* 2007; **56**: 373-379 [PMID: 17005766 DOI: 10.1136/gut.2006.099614]

12 **Wada Y**, Kashida H, Kudo SE, Misawa M, Ikehara N, Hamatani S. Diagnostic accuracy of pit pattern and vascular pattern analyses in colorectal lesions. *Dig Endosc* 2010; **22**: 192-199 [PMID: 20642608 DOI: 10.1111/j.1443-1661.2010.00983.x]

13 **Su MY**, Hsu CM, Ho YP, Chen PC, Lin CJ, Chiu CT. Comparative study of conventional colonoscopy, chromoendoscopy, and narrow-band imaging systems in differential diagnosis of neoplastic and nonneoplastic colonic polyps. *Am J Gastroenterol* 2006; **101**: 2711-2716 [PMID: 17227517 DOI: 10.1111/j.1572-0241.2006.00932.x]

14 **Tanaka S**, Sano Y. Aim to unify the narrow band imaging (NBI) magnifying classification for colorectal tumors: current status in Japan from a summary of the consensus symposium in the 79th Annual Meeting of the Japan Gastroenterological Endoscopy Society. *Dig Endosc* 2011; **23** Suppl 1: 131-139 [PMID: 21535219 DOI: 10.1111/j.1443-1661.2011.01106.x]

15 **Yoshida N**, Naito Y, Kugai M, Inoue K, Uchiyama K, Takagi T, Ishikawa T, Handa O, Konishi H, Wakabayashi N, Kokura S, Yagi N, Morimoto Y, Yanagisawa A, Yoshikawa T. Efficacy of magnifying endoscopy with flexible spectral imaging color enhancement in the diagnosis of colorectal tumors. *J Gastroenterol* 2011; **46**: 65-72 [PMID: 21061025 DOI: 10.1007/s00535-010-0339-9]

16 **Saito S**, Tajiri H, Ohya T, Nikami T, Aihara H, Ikegami M. Imaging by Magnifying Endoscopy with NBI Implicates the Remnant Capillary Network As an Indication for Endoscopic Resection in Early Colon Cancer. *Int J Surg Oncol* 2011; **2011**: 242608 [PMID: 22312499 DOI: 10.1155/2011/242608]

17 **Uraoka T**, Saito Y, Ikematsu H, Yamamoto K, Sano Y. Sano's capillary pattern classification for narrow-band imaging of early colorectal lesions. *Dig Endosc* 2011; **23** Suppl 1: 112-115 [PMID: 21535215 DOI: 10.1111/j.1443-1661.2011.01118.x]

18 **IJspeert JE**, Bastiaansen BA, van Leerdam ME, Meijer GA, van Eeden S, Sanduleanu S, Schoon EJ, Bisseling TM, Spaander MC, van Lelyveld N, Bargeman M, Wang J, Dekker E; Dutch Workgroup serrAted polypS & Polyposis (WASP). Development and validation of the WASP classification system for optical diagnosis of adenomas, hyperplastic polyps and sessile serrated adenomas/polyps. *Gut* 2016; **65**: 963-970 [PMID: 25753029 DOI: 10.1136/gutjnl-2014-308411]

19 **Singh R**, Jayanna M, Navadgi S, Ruszkiewicz A, Saito Y, Uedo N. Narrow-band imaging with dual focus magnification in differentiating colorectal neoplasia. *Dig Endosc* 2013; **25** Suppl 2: 16-20 [PMID: 23617643 DOI: 10.1111/den.12075]

20 **Rex DK**, Kahi C, O'Brien M, Levin TR, Pohl H, Rastogi A, Burgart L, Imperiale T, Ladabaum U, Cohen J, Lieberman DA. The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on real-time endoscopic assessment of the histology of diminutive colorectal polyps. *Gastrointest Endosc* 2011; **73**: 419-422 [PMID: 21353837 DOI: 10.1016/j.gie.2011.01.023]

21 **ASGE Technology Committee.**, Abu Dayyeh BK, Thosani N, Konda V, Wallace MB, Rex DK, Chauhan SS, Hwang JH, Komanduri S, Manfredi M, Maple JT, Murad FM, Siddiqui UD, Banerjee S. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting real-time endoscopic assessment of the histology of diminutive colorectal polyps. *Gastrointest Endosc* 2015; **81**: 502.e1-502.e16 [PMID: 25597420 DOI: 10.1016/j.gie.2014.12.022]

22 **Rex DK**, Ahnen DJ, Baron JA, Batts KP, Burke CA, Burt RW, Goldblum JR, Guillem JG, Kahi CJ, Kalady MF, O'Brien MJ, Odze RD, Ogino S, Parry S, Snover DC, Torlakovic EE, Wise PE, Young J, Church J. Serrated lesions of the colorectum: review and recommendations from an expert panel. *Am J Gastroenterol* 2012; **107**: 1315-29; quiz 1314, 1330 [PMID: 22710576 DOI: 10.1038/ajg.2012.161]

23 **Kumar S**, Fioritto A, Mitani A, Desai M, Gunaratnam N, Ladabaum U. Optical biopsy of sessile serrated adenomas: do these lesions resemble hyperplastic polyps under narrow-band imaging? *Gastrointest Endosc* 2013; **78**: 902-909 [PMID: 23849819 DOI: 10.1016/j.gie.2013.06.004]

24 **Tadepalli US**, Feihel D, Miller KM, Itzkowitz SH, Freedman JS, Kornacki S, Cohen LB, Bamji ND, Bodian CA, Aisenberg J. A morphologic analysis of sessile serrated polyps observed during routine colonoscopy (with video). *Gastrointest Endosc* 2011; **74**: 1360-1368 [PMID: 22018553 DOI: 10.1016/j.gie.2011.08.008]

25 **Hazewinkel Y**, López-Cerón M, East JE, Rastogi A, Pellisé M, Nakajima T, van Eeden S, Tytgat KM, Fockens P, Dekker E. Endoscopic features of sessile serrated adenomas: validation by international experts using high-resolution white-light endoscopy and narrow-band imaging. *Gastrointest Endosc* 2013; **77**: 916-924 [PMID: 23433877 DOI: 10.1016/j.gie.2012.12.018]

26 **Singh R**, Nordeen N, Mei SL, Kaffes A, Tam W, Saito Y. West meets East: preliminary results of narrow band imaging with optical magnification in the diagnosis of colorectal lesions: a multicenter Australian study using the modified Sano's classification. *Dig Endosc* 2011; **23** Suppl 1: 126-130 [PMID: 21535218 DOI: 10.1111/j.1443-1661.2011.01107.x]

27 **Yamashina T**, Takeuchi Y, Uedo N, Aoi K, Matsuura N, Nagai K, Matsui F, Ito T, Fujii M, Yamamoto S, Hanaoka N, Higashino K, Ishihara R, Tomita Y, Iishi H. Diagnostic features of sessile serrated adenoma/polyps on magnifying narrow band imaging: a prospective study of diagnostic accuracy. *J Gastroenterol Hepatol* 2015; **30**: 117-123 [PMID: 25088839 DOI: 10.1111/jgh.12688]

28 **Hassan C**, Pickhardt PJ, Rex DK. A resect and discard strategy would improve cost-effectiveness of colorectal cancer screening. *Clin Gastroenterol Hepatol* 2010; **8**: 865-869, 869.e1-869.e3 [PMID: 20621680 DOI: 10.1016/j.cgh.2010.05.018]

29 **Kessler WR**, Imperiale TF, Klein RW, Wielage RC, Rex DK. A quantitative assessment of the risks and cost savings of forgoing histologic examination of diminutive polyps. *Endoscopy* 2011; **43**: 683-691 [PMID: 21623556 DOI: 10.1055/s-0030-1256381]

30 **Zorron Cheng Tao Pu L,** Koay DSC, Ovenden A, Burt AD, Singh R. Prospective study predicting histology in colorectal lesions: Interim analysis of the NICE, JNET and MS classifications. *J Gastroenterol Hepatol* 2017; **32**: 252 [DOI: 10.1111/jgh.13881]

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Chapter 7

Comparison of different virtual chromoendoscopy classification systems for the characterization of colorectal lesions

This chapter offers a brief summary, as well as a copy of the paper accepted for publication in the *JGH Open* journal, complete with tables, figures, references and supplementary materials. The statement of authorship and manuscript copy of the submitted paper 'Comparison of different virtual chromoendoscopy classification systems for the characterization of colorectal lesions' follow over the page.

7.1 Summary

Although in Chapter 5 we demonstrated that MS was superior to NICE, at the time the study was designed our evaluation of MS was constrained by the lack of a category for SSA/Ps in the NICE classification. With the recent introduction of the WASP 'add-on' classification, a more complete investigation of the potential of MS became possible. In addition, another classification was created in recent years that is currently the gold-standard classification in the East–the JNET classification. Given these advances in the tools for CRC assessment, we conducted a two-centre study to compare the current cutting-edge NBI classifications for colorectal lesions.

Initially, patients undergoing colonoscopy at the Lyell McEwin Hospital (Adelaide, SA) were prospectively enrolled in the study, and when lesions were found, these were assessed for all classifications in real-time (exploratory phase). While the MS classification can differentiate SSA/Ps on its own, the NICE and JNET classifications were combined with WASP for this purpose (named wNICE and wJNET, respectively).

In sequence, a validation phase took place where lesions on NBI and blue laser imaging (BLI) were assessed ex-vivo by four external endoscopists in Japan. 483 colorectal lesions were evaluated by the two investigators in the exploratory phase and 30 colorectal lesion images were evaluated independently by each endoscopist in the validation phase. The results have shown that MS accuracy is superior to other classifications, even when simplified to a 4-type or 3-type classification. The better results of the MS classification were corroborated by the validation phase, with both NBI and BLI images.

More research is warranted to demonstrate the reproducibility of these results in other endoscopy centres, especially having in mind that both participant centres were academic centres with substantial expertise in advanced endoscopic imaging. Nevertheless, these results are encouraging and allow us to envision a future where the use of comprehensive classifications inclusive of serrated lesions differentiation becomes the standard of practice.

7.2 Statement of authorship

Statement of Authorship

Title of Paper	Comparison of different virtual chromoendoscopy classification systems for the characterisation of colorectal neoplasia
Publication Status	☐ Published ☑ Accepted for Publication ☑ ~~Submitted for Publication~~ ☐ Unpublished and Unsubmitted work written in manuscript style
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Principal Author

Name of Principal Author (Candidate)	Leonardo Zorron Cheng Tao Pu		
Contribution to the Paper	Conceptualised and designed the study. Involved in data collection (exploratory and validation phases), processing and statistical analyses. Interpreted the results and prepared the manuscript.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	10/12/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Takeshi Yamamura		
Contribution to the Paper	Involved in data collection (validation phase), interpretation and critical manuscript revision for important intellectual content. Revised, read and approved the final version of the manuscript.		
Signature		Date	28/12/2019

Name of Co-Author	Masanao Nakamura		
Contribution to the Paper	Involved in data collection (validation phase), interpretation and critical manuscript revision for important intellectual content. Revised, read and approved the final version of the manuscript.		
Signature		Date	28/12/2019

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Signature		Date	12/12/19

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Name of Co-Author	Suzanne Edwards		
Contribution to the Paper	Involved in statistical analysis and interpretation of results. Revised, read and approved the final version of the manuscript.		
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Name of Co-Author	Alastair D Burt		
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Name of Co-Author	Yoshiki Hirooka		
Contribution to the Paper	Involved in data interpretation and critical manuscript revision for important intellectual content. Revised, read and approved the final version of the manuscript.		
Signature		Date	Dec. 23. 2019

Name of Co-Author	Mitsuhiro Fujishiro		
Contribution to the Paper	Involved in data interpretation and critical manuscript revision for important intellectual content. Revised, read and approved the final version of the manuscript.		
Signature		Date	Dec 26, 2019

Name of Co-Author	Rajvinder Singh		
Contribution to the Paper	Conceptualised and designed the study. Involved in data interpretation and critical manuscript revision for important intellectual content. Revised, read and approved the final version of the manuscript.		
Signature		Date	02/01/2020

7.3 Paper accepted by *JGH Open*

Comparison of different virtual chromoendoscopy classification systems for the characterization of colorectal lesions

Abstract

Background and Aim: Commonly-used classifications for colorectal lesions (CLs) include the Narrow Band Imaging (NBI) International Colorectal Endoscopic (NICE) and Japan NBI Expert Team (JNET) classifications. However, both lack a sessile serrated adenoma/polyp (SSA/P) category. This has been addressed by the modified Sano's (MS) and Workgroup serrAted polypS and Polyposis (WASP) classifications. This study aims to compare the accuracy of wNICE and wJNET (WASP added to both) with the stand-alone MS classification.

Methods: Patients undergoing colonoscopy at an Australian tertiary hospital who had at least one CL detected were prospectively enrolled. In the exploratory phase, CLs were characterized in real-time with NBI and magnification using all classifications. In the validation phase, CLs were assessed with both NBI and Blue Laser Imaging (BLI) by four external endoscopists in Japan. The primary outcome was the comparison of wJNET and MS. Secondary outcomes included comparisons amongst all classifications and the calculation of inter-rater reliability.

Results: 483 CLs were evaluated in real-time in exploratory phase; and four sets of 30 CL images (80 on NBI and 40 on BLI) were scored in the validation phase. For high-confidence diagnoses, MS accuracy was superior to wJNET in both the exploratory (86% versus 79%, $p<0.05$) and validation (85% versus 69%, $p<0.05$) phases. The inter-rater reliability was substantial for all classifications (kappa = 0.74, 0.69 and 0.63 for wNICE, wJNET and MS respectively).

Conclusions: MS classification achieved the highest accuracy in both exploratory and validation phases. MS can differentiate serrated and adenomatous polyps as a stand-alone classification.

Keywords: Colonoscopy; colorectal neoplasms; serrated polyp; adenoma

Introduction

Screening programs based on fecal tests and colonoscopy have been implemented to tackle the scourge of colorectal cancer (CRC). The efficacy of such programs relies on the detection of CRC precursors. Initially, screening programs were specifically designed to detect and remove adenomatous polyps, which have been thought for decades to be the sole precursors leading to CRC. However, the appearance of "missed" CRCs promoted a search for other explanations and the role of serrated polyps in CRC carcinogenesis emerged.

Sessile serrated adenomas/polyps (SSA/Ps) have been shown to contribute to up to a third of CRCs, contrasting with the fact that they have a low reported prevalence in both the East and West (1, 2). The discrepancy between the prevalence of SSA/Ps and their share of responsibility for CRC may be explained by the fact that the serrated pathway has a higher risk of developing CRC than the traditional adenoma-carcinoma pathway (3). This may be due to a more "aggressive" pathophysiology (4). However, it is also possible that the difficulty in detecting and characterising SSA/Ps (misdiagnosing it to be non-neoplastic) could be one of the reasons for its low prevalence.

Although image enhancing endoscopy technologies have proven to be effective in identifying and discriminating adenomatous polyps from other colorectal lesions (CLs), the differentiation of serrated lesions is more challenging. Hyperplastic polyps (HPs) are usually considered to be benign and could potentially be left *in situ* when smaller than 5 mm and restricted to the rectosigmoid region (5, 6). A meta-analysis showed that despite promising results with Narrow Band Imaging (NBI), more data is needed to confirm the use of image enhancing endoscopy as a useful tool for SSA/Ps (7). Nevertheless, NBI appears to be the most promising technology for this and has met the thresholds of the American Society for Gastrointestinal Endoscopy (ASGE) Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) program (5).

The use of NBI has been studied by several experts with a variety of classifications including the Sano, Modified Sano's (MS), Hiroshima, Japan NBI Expert Team (JNET), Showa, Jikei, NBI International Colorectal Endoscopic (NICE) and Workgroup serrAted polypS and Polyposis (WASP) classifications. JNET (Supplementary Figure 1) has been recently proposed in Japan as an amalgamation of all Japanese classifications (8). NICE (Supplementary Figure 2) is still one of the most widely used classifications (especially in the West), probably due to its simplicity and practicality. However, recently MS was found to outperform the NICE classification (9). The MS classification was conceived in 2013 and consists of 5 categories (I, IIo, II, IIIa and IIIb), while JNET has 4 (1, 2A, 2B and 3) and NICE has 3 (1, 2 and 3). Of all these classifications, only WASP and MS are able to classify SSA/Ps into a separate category (8-14). Other classifications assign SSA/Ps alongside HPs, hence mixing neoplastic with non-neoplastic polyps. As the role of the serrated

pathway becomes clearer, the use of an endoscopic classification that could characterize SSA/Ps is important. The use of endoscopic classifications that cannot differentiate HPs from SSA/Ps might lead to the decision of leaving a neoplastic polyp what can contribute to interval CRC.

The aim of this study was to compare the accuracy of the three endoscopic classifications with the ability to differentiate serrated polyps: NICE and JNET combined with WASP (wNICE and wJNET, respectively) and the MS classification.

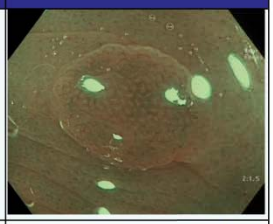
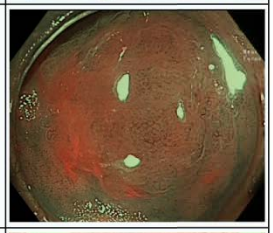
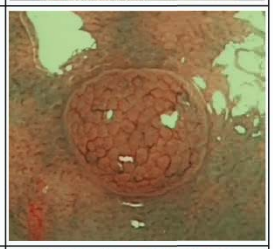
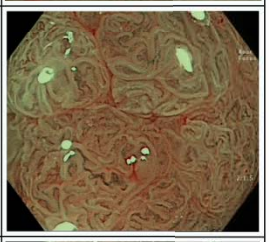
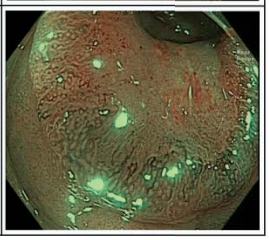
Methods

Patients undergoing an elective colonoscopy at the Lyell McEwin Hospital, South Australia (August 2016 to January 2018), were prospectively enrolled in the 'exploratory phase'. All procedures were performed by an expert in image enhancing endoscopy (RS), with over 10 years of experience in advanced imaging, using the Olympus® 190 series (Exera III) colonoscopes. Patients under 18 years of age, those undergoing emergency colonoscopy, pregnant women, those with total colectomy, a previous or new diagnosis of inflammatory bowel disease (IBD), with no CLs identified, with familial adenomatous polyposis syndrome or Peutz-Jeghers syndrome were excluded, as were those unwilling to participate. In addition, polyps that were detected and resected but not confirmed by histology (i.e. normal mucosa, melanosis coli or not retrieved); and patients who could not have a colonoscopy completed (e.g. poor bowel preparation) were excluded.

After a CL was detected with white light, NBI with magnification was used to characterise the lesion. This was performed with the aid of a transparent soft distal attachment cap (©Olympus D201). Two endoscopists (the endoscopist who was performing the procedure and a colleague) evaluated the characteristics of all CLs in real-time during the procedure. These included size, Paris classification, serrated features, JNET, MS and NICE classifications. Serrated features included the 4 characteristics described by the WASP classification (Supplementary figure 3) in addition to 2 other features – varicose microvascular vessels (VMV) and presence of a mucous cap as per the MS classification. The utilization of WASP as a workup to characterize SSA/Ps for both JNET (from types 1 and 2A) and NICE (from types 1 and 2) was based on the original WASP publication (13). All polyps found during the study were removed for histopathological analysis.

For diagnoses made with high confidence, there had to be agreement between the both endoscopists (RS and LZCTP). Although no specific training was done for this study, both were familiar with all classifications prior to the study. After both endoscopists were content that enough visualization with magnified NBI has been done on the lesion, they would call the predicted types for each classification. If the predicted types matched, it would be called as a high confidence diagnosis. If not, the prediction of the senior endoscopist (RS) prevailed as low confidence. For wNICE types 1 and 2; and wJNET types 1 and 2A, the initial classification diagnosis

was converted into SSA/P if two or more of the WASP features were found. For the MS classification categories I and II, the confidence level was also based on the serrated features which were detected (Figure 1).

MS classification (predicted histology)	Description	Example
MS I (HP - hyperplastic polyp)	Pale colour ± round pits with central brown star-like dots or bland appearance ± minute capillaries that may meander across polyp	
MS IIo (SSA/P - sessile serrated adenoma/polyp)	Pale or light dark colour ± open pits ± 3 out of 5: cloud-like surface, inconspicuous margins, mucous cap, irregular shape and varicose microvascular vessels	
MS II (tubular adenoma with low grade dysplasia)	Light dark or dark colour ± white linear or oval pits ± linear or oval regular capillary network surrounding pits	
MS IIIa (high grade dysplasia‡/ villous or tubulovillous adenoma/superficial cancer)	Light dark or dark colour ± white villous/cerebriform pits ± tortuous/branched mildly regular capillary network surrounding pits§	
MS IIIb (invasive cancer)	Dark surroundings with pale central area ± loss of pit and vascular pattern	

‡High-grade dysplastic SSA/Ps are included in this category
§May have slight loss of pit pattern and vascularity when leaning towards superficial cancer

Figure 1 – MS classification (adapted from Pu et al., 2018[9])

'Open pits' feature was considered to be a high-confidence feature by itself (i.e. independent SSA/P feature). The remaining five serrated features were considered as interdependent SSA/P features and their definition were as follow: MS I with high confidence for HP if "NO" for any serrated features; MS I with low confidence for HP if up to one "YES" for interdependent serrated features; MS IIo with low confidence for SSA/P if "YES" for two interdependent serrated features; and MS IIo with high confidence for SSA/P if "YES" for open pits or at least three "YES" for interdependent serrated features. This decision tree has been illustrated in a diagram for easier understanding (Figure 2).

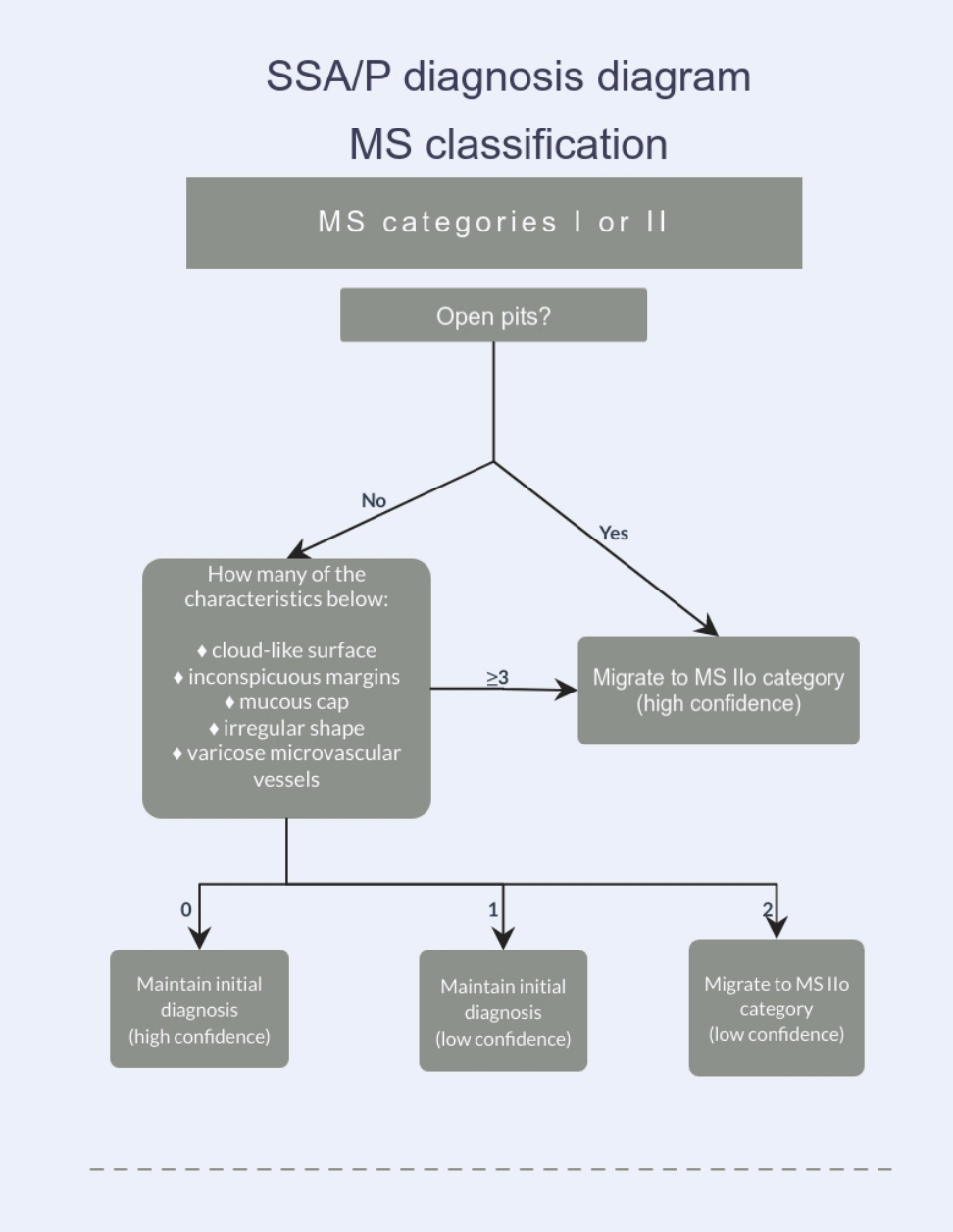


Figure 2 – SSA/P diagnosis diagram for the MS classification

All diagnoses were compared with the final histopathological report. In our institution, all polyps are evaluated by a general pathologist who seeks the input of a specialist gastrointestinal pathologist only if uncertain of the diagnosis. The criteria for diagnosis of SSA/Ps was based on the World Health Organization recommendations and consisted of at least 2 of the following criteria: i) crypt dilation, ii) irregularly branching crypts and iii) horizontally arranged basal area crypts at the basal (inverted T and/or L-shaped crypts)(15). Neoplastic lesions were considered as any CL that had the potential or had already evolved into a CRC (i.e. tubular adenoma, tubulovillous adenoma, villous adenoma, traditional serrated adenoma, SSA/P, superficial adenocarcinoma or invasive adenocarcinoma). The differentiation of high-grade dysplasia (HGD), superficial cancer and invasive cancer was adopted using as limits for the severely dysplastic cells at the muscularis

mucosae, 1000 micrometers into the submucosa and the muscularis propria, respectively(16, 17). CLs with 5 mm or less were considered as diminutive in size.

After all data from the exploratory phase of the study had been collected, 20 CLs' NBI magnified images were chosen from the Australian database. These were selected in order to be representative of all histological classes and varied in size (half ≤5 mm and half ≥10 mm). 10 additional images were collected from the Nagoya University Hospital electronic database and correlated with histology. These 10 images were captured by a Fujifilm 600 series colonoscope (©Fujifilm Corporation Japan), with BLI and magnification. In the validation phase, 4 experienced endoscopists (more than 5 years of experience with advanced imaging and magnification and part of the lower gastrointestinal endoscopy unit) were invited to participate in a 60-minute session. The study was explained, with emphasis on how to use all classifications. The 4 endoscopists selected for the validation phase had no clinical experience and little knowledge of the MS classification prior to the study; but were familiar to the NICE, WASP and JNET classifications.

The design of the study has been summarised into a flowchart for better understanding (Figure 3, over page).

The primary outcome was the comparison of high-confidence accuracy for wJNET and MS (5-type classifications). Secondary outcomes included comparison of a 2-type classifications (i.e. dichotomy of neoplastic versus non-neoplastic with wNICE, wJNET and MS), 4-type classifications (i.e. wNICE, merged wJNET and merged MS), an external validation of the classifications with NBI and BLI images, and sub-analysis of specific datasets (i.e. high-confidence accuracy, lesions ≤ 5 mm, lesions on NBI and lesions on BLI). As wNICE is a 4-type classification and wJNET and MS 5-type classifications, the two adenoma categories in wJNET and MS were merged into a single category (2A+2B and II+IIIa, respectively) when compared to wNICE.

The sample size was calculated based on number of CLs against the primary outcome for the exploratory phase. An estimated sample size of 423 CLs would be required to have an 80% power with an alpha error of 0.05 to appreciate an increment of 6% in the prediction of histology with the MS classification (from 86% to 92%). This increment was inferred as slightly lower than what was found in our previous study for the comparison of MS versus NICE(9). A McNemar test was used for comparison of accuracies for dichotomic classifications in the exploratory phase, two by two. Comparison of proportions was done with Chi-squared test in both exploratory and validation phases. A p-value<0.05 was considered significant. Wilson score method without continuity correction was used to calculate 95% confidence interval for proportions(18).

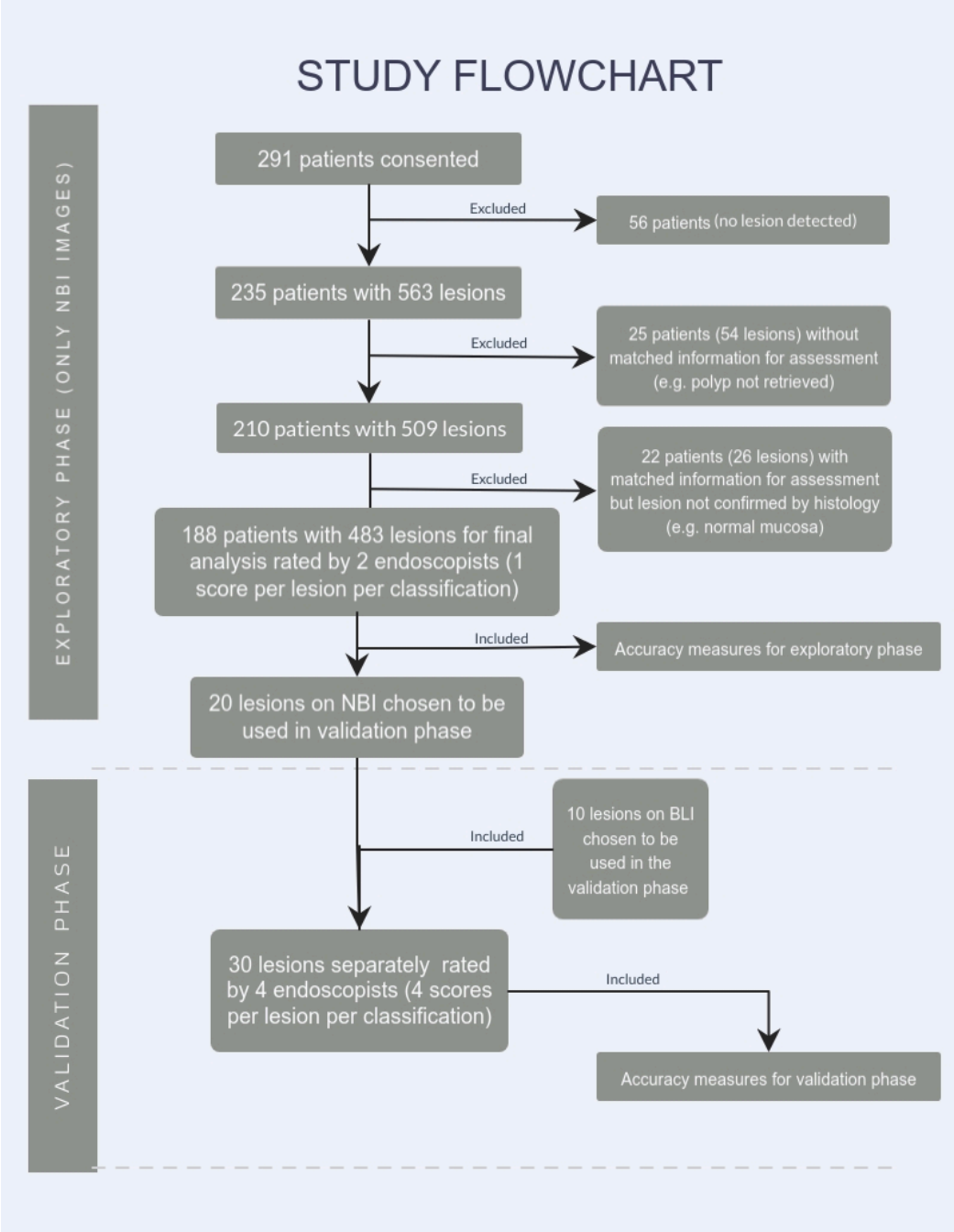


Figure 3 – Study flowchart

Fleiss' kappa was used for interobserver agreement among the 4 endoscopists in the validation phase and was interpreted as: < 0.01 = poor agreement; 0.01 to 0.20 = slight agreement; 0.21 to 0.40 = fair agreement; 0.41 to 0.60 = moderate agreement; 0.61 to 0.80 = substantial agreement; and 0.81 to 1.00 = almost perfect agreement (19).This study and the use of endoscopy images were approved by the Human Research Ethics Committee (TQEH/LMH/MH/2008128) in Australia and by the Nagoya University Hospital Ethics Review Committee (2015-0485) in Japan. This study is presented in accordance to the STROBE statement(20).

Results

As per the inclusion and exclusion criteria, a total of 291 patients were consented. From those, 56 were excluded due to intra-procedure exclusion criteria. From the 235 remaining, 25 patients (54 CLs) had insufficient data for assessment (e.g. polyp not able to be retrieved). Furthermore, 26 CLs from 22 patients were not confirmed at histology (e.g. melanosis coli) and were hence excluded. In the validation phase, a set of 20 CLs with were chosen from the exploratory phase and 10 CLs were selected from a histology-correlated Japanese image database. The CLs chosen for the validation phase were evenly distributed amongst the 5 types predicted by MS and wJNET.

For the final analysis of the exploratory phase, 188 patients with 483 polyps were evaluated. Most of the evaluated polyps were adenomas (Table 1). Overall, more than 90% were called with high confidence by all classifications in the exploratory phase (98.3% with wNICE, 98.3% with wJNET and 94.8% with MS). For wJNET and MS, the overall accuracies were 78.5% and 83.6% respectively (p=0.04) while the high-confidence accuracies were 79.2% and 85.6% respectively (p=0.01).

Table 1 – Polyp histology and correlation with classifications' types

<table>
<tr><th rowspan="2">HISTOLOGY – N (%)</th><th rowspan="2">Exploratory phase</th><th rowspan="2">Validation phase[◆]</th><th colspan="3">Correlation with classifications' type</th></tr>
<tr><th>wNICE</th><th>wJNET</th><th>MS</th></tr>
<tr><td>Hyperplastic</td><td>56 (11.6)</td><td>24 (20.0)</td><td>1</td><td>1</td><td>I</td></tr>
<tr><td>Tubular adenoma LGD</td><td>237 (49.1)</td><td>28 (23.3)</td><td rowspan="6">2</td><td rowspan="3">2A</td><td>II</td></tr>
<tr><td>Tubulovillous adenoma LGD</td><td>58 (12.0)</td><td>8 (6.7)</td><td rowspan="5">IIIa</td></tr>
<tr><td>Villous adenoma LGD</td><td>3 (0.6)</td><td>0 (0)</td></tr>
<tr><td>Tubular adenoma HGD</td><td>5 (1.0)</td><td>0 (0)</td><td rowspan="3">2B</td></tr>
<tr><td>Tubulovillous adenoma HGD</td><td>15 (3.1)</td><td>16 (13.3)</td></tr>
<tr><td>Villous adenoma HGD</td><td>2 (0.4)</td><td>0 (0)</td></tr>
<tr><td>SSA/P no dysplasia</td><td>75 (15.5)</td><td>24 (20.0)</td><td rowspan="3">1 or 2[‡]</td><td>1 or 2A[‡]</td><td>I/II[‡] or IIo</td></tr>
<tr><td>SSA/P LGD</td><td>8 (1.7)</td><td>0 (0.0)</td></tr>
<tr><td>SSA/P HGD</td><td>2 (0.4)</td><td>4 (3.3)</td><td rowspan="2">2B</td><td rowspan="2">IIIa</td></tr>
<tr><td>Superficial cancer</td><td>6 (1.2)</td><td>0 (0.0)</td><td>2</td></tr>
<tr><td>Invasive cancer</td><td>11 (2.3)</td><td>16 (13.3)</td><td>3</td><td>3</td><td>IIIb</td></tr>
<tr><td>Other</td><td>5 (1.0)</td><td>0 (0)</td><td>-</td><td>-</td><td>-</td></tr>
</table>

LGD – low grade dysplasia
HGD – high grade dysplasia
SSA/P – sessile serrated adenoma/polyp
[◆]N based on the number of images evaluated by the 4 endoscopists
[‡]Dependent on serrated features as per the WASP and MS classification

When early/low-grade dysplasia (LGD) and advanced/HGD adenoma categories were merged, the comparison between wNICE, merged wJNET and merged MS was made possible and achieved 88.2%, 88.2% and 88.8% overall accuracy, respectively. For high-confidence diagnoses, once more the accuracy was

numerically higher for the MS classification, but this difference did not achieve statistical significance (Figure 4). The subgroup analysis of only diminutive polyps showed similar results to the whole cohort (Table 2). When evaluating the ability to predict neoplastic versus non-neoplastic lesions, the accuracy for wNICE, wJNET and MS all surpassed 90% (Table 3). Although the NPV value did not reach 90% with any of the classifications, this analysis was not restricted to the rectosigmoid region.

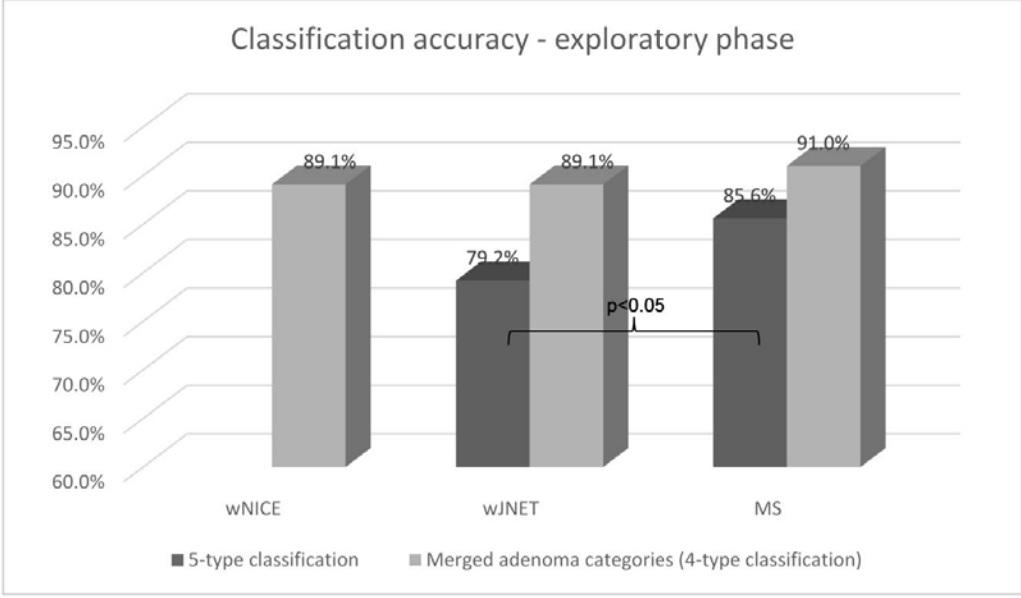


Figure 4 – Accuracy for all data with high confidence (exploratory phase)

Table 2 – Accuracy of 4 and 5-type classifications for all data and subsets for exploratory phase

	Overall accuracy % (95% confidence interval)			**High-confidence accuracy** % (95% confidence interval)		
Classification	wNICE	wJNET	MS	wNICE	wJNET	MS
All data	88.2 (85.0;90.8)	78.5 (74.6;81.9)	83.6 (80.0;86.6)	89.1 (86.0;91.6)	79.2 (75.3;82.6)	85.6 (82.1;88.5)
All data with adenoma categories merged	N/A	88.2 (85.0;90.8)	88.8 (85.7;91.3)	N/A	89.1 (86.0;91.6)	91.0 (88.0;93.3)
N	483	483	483	475	475	458
≤5mm subset	86.4 (81.4;90.2)	85.6 (80.6;89.5)	86.4 (81.4;90.2)	87.4 (82.5;91.1)	86.5 (81.5;90.3)	88.1 (83.1;91.7)
≤5mm subset with adenoma categories merged	N/A	86.4 (81.4;90.2)	86.9 (82.0;90.6)	N/A	87.4 (82.5;91.1)	88.6 (83.7;92.2)
N	236	236	236	230	230	219

Table 3 – Accuracy measures for dichotomy neoplastic versus non-neoplastic for high-confidence diagnosis (exploratory phase)

	Overall diagnosis % (95% confidence interval)			High-confidence diagnosis % (95% confidence interval)		
Classification	wNICE	wJNET	MS	wNICE	wJNET	MS
Accuracy	90.3 (87.3;92.6)	90.3 (87.3;92.6)	90.7 (87.8;93.0)	90.7 (87.8;93.0)	90.7 (89.0;94.0)	93.0 (90.3;95.0)
Sensitivity	95.3 (93.0;96.9)	95.3 (93.0;96.9)	96.2 (94.1;97.6)	95.7 (93.5;97.2)	95.7 (93.5;97.2)	98.3 (96.7;99.2)
Specificity	55.0 (50.5;59.4)	55.0 (50.5;59.4)	51.7 (47.3;56.1)	55.9 (51.4;60.3)	55.9 (51.4;60.3)	46.8 (42.3;51.4)
Positive predictive value	93.7 (91.2;95.5)	93.7 (91.2;95.5)	93.3 (90.7;95.2)	93.9 (91.4;95.7)	93.9 (91.4;95.7)	94.2 (91.7;96.0)
Negative predictive value	62.3 (57.9;66.5)	62.3 (57.9;66.5)	66.0 (61.7;70.1)	64.7 (60.3;68.9)	64.7 (60.3;68.9)	75.9 (71.8;79.6)

The description of misdiagnoses predicted by wNICE, wJNET and MS classifications are shown in Supplementary Tables 1 to 3 for the exploratory phase and in Supplementary Tables 4 to 6 for the validation phase. In these tables, the misdiagnoses were divided into severe and moderate. Severe misdiagnoses are highlighted in red and were considered when they would have led to a major change in the therapeutic decision (i.e. non-resection of a neoplastic polyp; endoscopic resection of an invasive cancer; or referral for surgery of a non-invasive cancer/benign lesion). Moderate misdiagnoses are highlighted in yellow and were defined as misdiagnoses that might lead to minor therapeutic changes (e.g. resection of a non-neoplastic polyp or resection of a superficially invasive cancer with endoscopic mucosal resection instead of endoscopic submucosal dissection).

The color green highlights the correct diagnoses. The rate of severe misdiagnoses for wNICE, wJNET and MS were 4.4%, 4.4% and 2.2% for high-confidence diagnosis, respectively. The rate of moderate misdiagnoses for the same classifications were 6.5%, 16.4% and 12.2% for high-confidence diagnosis, respectively. There was a statistically significant difference between wNICE and the other two classifications regarding moderate misdiagnoses alone ($p<0.01$). This is likely attributed to the inability of the NICE classification to differentiate subtypes of adenomas (e.g. both a low-grade tubular adenoma and a high-grade tubulovillous adenoma would be "accurately" classified as a NICE type 2).

In the validation phase, 4 experienced endoscopists evaluated 30 CL images each. The final dataset of 120 images scored for all classifications consisted of NBI and BLI subsets (80 and 40 images, respectively). Details on histology can be found in Table 1. The results of this phase (high-confidence accuracy) for the whole dataset and NBI subset confirmed the significantly higher accuracy of MS compared to wJNET found in the exploratory phase (Figure 5). Accuracy performance for the subset of NBI data can be found in Table 4 and Supplementary Figure 4.

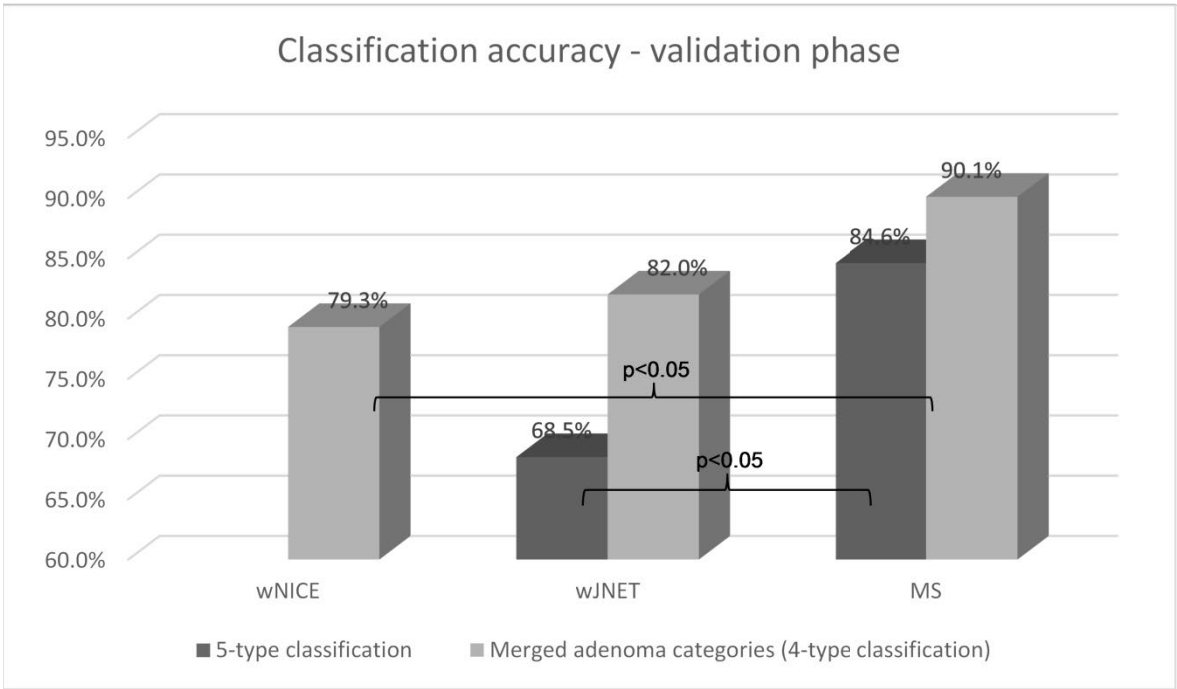


Figure 5 – Accuracy for all data with high confidence (validation phase)

Table 4 – Accuracy of 4 and 5-type classifications for all data and subsets for validation phase

	Overall accuracy % (95% confidence interval)			**High-confidence accuracy** % (95% confidence interval)		
Classification	wNICE	wJNET	MS	wNICE	wJNET	MS
All data	N/A	70.0 (61.3;77.5)	81.7 (73.8;87.6)	N/A	68.5 (59.4;76.4)	84.6 (75.8;90.6)
All data with adenoma categories merged	79.2 (71.1;85.5)	83.3 (75.6;88.9)	89.2 (82.4;93.6)	79.3 (70.9;85.8)	82.0 (73.8;88.0)	90.1 (82.3;94.7)
N	120	120	120	111	111	91
NBI subset	N/A	65.0 (54.1;74.6)	77.5 (67.2;85.3)	N/A	63.0 (51.5;73.2)	81.4 (69.7;89.3)
NBI subset with adenoma categories merged	77.5 (67.2;85.3)	80.0 (70.0;87.3)	87.5 (78.5;93.1)	77.5 (66.5;85.7)	78.1 (67.3;86.1)	89.8 (79.5;95.2)
N	80	80	80	71	73	59
≤5mm subset	N/A	67.5 (52.0;79.9)	80.0 (65.2;89.5)	N/A	65.7 (49.1;79.2)	85.7 (68.5;94.3)
≤5mm subset with adenoma categories merged	77.5 (62.5;87.7)	80.0 (65.2;89.5)	90.0 (77.0;96.0)	77.8 (61.9;88.3)	77.1 (60.9;87.9)	92.9 (77.4;98.0)
N	40	40	40	36	35	28
BLI subset	N/A	80.0 (65.2;89.5)	90.0 (77.0;96.0)	N/A	78.9 (63.6;88.9)	90.6 (75.8;96.8)
BLI subset with adenoma categories merged	82.5 (68.1;91.3)	90.0 (77.0;96.0)	92.5 (80.1;97.4)	82.5 (68.1;91.3)	89.5 (75.9;95.8)	90.6 (75.8;96.8)
N	40	40	40	40	38	32

Interobserver agreement between the 4 endoscopists in the validation phase achieved substantial agreement for the whole dataset with kappa values of 0.74, 0.69 and 0.63 for NICE, JNET and MS, respectively. For the high-confidence subset the agreement found was almost perfect (κ=0.82), substantial (κ=0.79) and moderate (κ=0.49) for NICE, JNET and MS, respectively. The variability of results among endoscopists for each classification was not statistically significant.

Discussion

The MS classification was already shown to have higher accuracy when compared to NICE classification for differentiating neoplastic from non-neoplastic polyps (10). However, in this previous study, SSA/Ps diagnosed as type 1 were excluded to mitigate the bias towards MS. This likely impaired the evaluation of MS's true potential. Therefore in this study we included the WASP classification (13) as an "add-on" for an adequate comparison between the current state-of-the-art classifications.

The main outcome was to compare classifications that could both differentiate HPs from SSA/Ps and early from advanced adenomas (i.e. wJNET and MS classifications). The MS classification was the most accurate classification between the two. This was also verified in the external validation phase which found a higher overall and high-confidence accuracy for MS compared to wJNET ($p=0.04$ and $p<0.01$, respectively). Although a numerically higher accuracy was found for the MS within the BLI subset, this did not reach statistical significance most likely due to the small numbers.

The use of a classification with the ability to differentiate advanced adenomas is important as this may have implications on the resection technique to be used. We hypothesise that the differences found between MS and wJNET were due to how the adenomas are divided within each classification. JNET divides adenomas based on the grade of dysplasia they exhibit (2A = low-grade dysplasia/low-grade intramucosal neoplasia; and 2B = high-grade dysplasia/high-grade intramucosal neoplasia or shallow submucosal invasive cancer). MS however separates adenomas based on ‘early’ or ‘advanced adenomas’: tubular adenomas with low grade dysplasia - MS II; advanced adenomas (e.g. villous adenomas or tubular adenomas with high grade dysplasia) are allocated in category IIIa. Our hypothesis is that this slightly different definition may have led to better accuracy results.

In the study, adenoma categories were merged in JNET and MS classifications for adequate comparison with wNICE. This was used as a tool to separately identify the contribution of the WASP criteria to NICE/JNET compared to the MS criteria in differentiating SSA/Ps. Although a slight difference was found in the exploratory phase, a more pronounced difference was found in the validation phase (Figure 5). The increased accuracy of MS may relate to how the SSA/P criteria differs in each classification. WASP includes 4 serrated features that are equally considered when

characterizing polyps (≥2 features = SSA/P - Supplementary figure 3). As per the MS, 6-serrated features are evaluated where the "open pits" feature is considered sufficient to call a SSA/P with high confidence by itself (Figure 2). These differences may have led to better results with the MS classification. An interesting subject for future research would be to analyse the performance of the JNET classification when taking into account all 6 serrated features as per MS, what could be considered a "modified JNET".

Although the study was validated with external endoscopists and BLI technology, the results might not be representative of all endoscopy centres as accuracy of endoscopic classifications depends on the setting it is evaluated (21). Nonetheless, we were able to show that potentially MS can extrapolate geographical boundaries and imaging systems. This has been also shown in another study from our group where computer-aided diagnosis was accurate with both NBI and BLI technologies (22). Another study shows the potential of using NBI-based classifications with BLI technology (23). Another limitation to our study is that all CLs were rated for all features/classifications by the same two endoscopists in the same room at the same time, which could lead to bias. An ideal design would have consisted in a larger number of endoscopists in different endoscopy suites. Finally, in our study we have used distal caps routinely. Although we believe it makes characterization with magnified NBI easier, it is not obligatory for using any of the classifications.

In conclusion, MS can differentiate serrated and adenomatous polyps as a stand-alone classification. This classification could be beneficial as an 'all-encompassing single classification' rather than using the NICE, JNET or combination of them (wNICE, wJNET) which could be impractical and confusing.

References

1. Laird-Fick HS, Chahal G, Olomu A, Gardiner J, Richard J, Dimitrov N. Colonic polyp histopathology and location in a community-based sample of older adults. BMC Gastroenterology. 2016;16(1):1-7.
2. Kawasaki K, Kurahara K, Yanai S, Oshiro Y, Yao T, Kobayashi H, et al. Colonoscopic features and malignant potential of sessile serrated adenomas: comparison with other serrated lesions and conventional adenomas. Colorectal Dis. 2016.
3. Erichsen R, Baron JA, Hamilton-Dutoit SJ, Snover DC, Torlakovic EE, Pedersen L, et al. Increased Risk of Colorectal Cancer Development Among Patients With Serrated Polyps. Gastroenterology. 2016;150(4):895-902.e5.
4. Bettington M, Walker N, Rosty C, Brown I, Clouston A, McKeone D, et al. Clinicopathological and molecular features of sessile serrated adenomas with dysplasia or carcinoma. Gut. 2015.
5. Abu Dayyeh BK, Thosani N, Konda V, Wallace MB, Rex DK, Chauhan SS, et al. ASGE Technology Committee systematic review and meta-analysis assessing

the ASGE PIVI thresholds for adopting real-time endoscopic assessment of the histology of diminutive colorectal polyps. Gastrointestinal Endoscopy. 2015;81(3):502.e1-.e16.

6. Ponugoti P, Lin J, Odze R, Snover D, Kahi C, Rex DK. Prevalence of sessile serrated adenoma/polyp in hyperplastic-appearing diminutive rectosigmoid polyps. Gastrointest Endosc. 2017;85(3):622-7.
7. Parikh ND, Chaptini L, Njei B, Laine L. Diagnosis of sessile serrated adenomas/polyps with image-enhanced endoscopy: a systematic review and meta-analysis. Endoscopy. 2016;48(8):731-9.
8. Sano Y, Tanaka S, Kudo S-e, Saito S, Matsuda T, Wada Y, et al. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. Digestive Endoscopy. 2016;28(5):526-33.
9. Pu LZCT, Cheong KL, Koay DSC, Yeap SP, Ovenden A, Raju M, et al. Randomised controlled trial comparing modified Sano's and narrow band imaging international colorectal endoscopic classifications for colorectal lesions. World journal of gastrointestinal endoscopy. 2018;10(9):210-8.
10. Yeap SP, Singh R, Ovenden A, Ruszkiewicz A, Lau JY, Rerknimitr R, et al. Sa1557 A Randomised Controlled Trial Comparing the Modified Sano's Versus the Nice Classifications Using Narrow Band Imaging With Near Focus Magnification in Differentiating Colorectal Polyps. Gastrointestinal Endoscopy. 2015;81(5, Supplement):AB259-AB60.
11. Kuruvilla N, Paramsothy R, Gill R, Selby WS, Remedios ML, Kaffes AJ. A prospective dual-center proof-of-principle study evaluating the incremental benefit of narrow-band imaging with a fixed zoom function in real-time prediction of polyp histology. Can we resect and discard? Gastrointest Endosc. 2015;82(2):362-9.
12. Hayashi N, Tanaka S, Hewett DG, Kaltenbach TR, Sano Y, Ponchon T, et al. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the Narrow-Band Imaging International Colorectal Endoscopic (NICE) classification. Gastrointestinal Endoscopy.78(4):625-32.
13. IJspeert JE, Bastiaansen BA, van Leerdam ME, Meijer GA, van Eeden S, Sanduleanu S, et al. Development and validation of the WASP classification system for optical diagnosis of adenomas, hyperplastic polyps and sessile serrated adenomas/polyps. Gut. 2016;65(6):963-70.
14. Singh R, Jayanna M, Navadgi S, Ruszkiewicz A, Saito Y, Uedo N. Narrow-band imaging with dual focus magnification in differentiating colorectal neoplasia. Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society. 2013;25 Suppl 2:16-20.
15. Snover D, Ahnen D, Burt R, Odze R. WHO Classification of tumours. Pathology and genetics. Tumours of Digestive System. Berlin: Springer; 2010.
16. Bosman FT CF, Hruban RH, Theise ND, editors. . WHO Classification of Tumours of the Digestive System. Lyon: IARC2010.

17. Ferlitsch M, Moss A, Hassan C, Bhandari P, Dumonceau JM, Paspatis G, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2017;49(3):270-97.

18. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in medicine. 1998;17(8):857-72.

19. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.

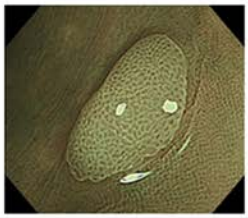
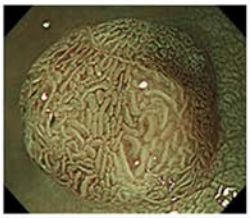
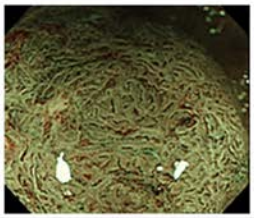
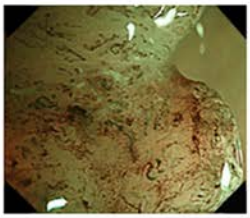
20. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7.

21. Rees CJ, Rajasekhar PT, Wilson A, Close H, Rutter MD, Saunders BP, et al. Narrow band imaging optical diagnosis of small colorectal polyps in routine clinical practice: the Detect Inspect Characterise Resect and Discard 2 (DISCARD 2) study. Gut. 2017;66(5):887-95.

22. Zorron Cheng Tao Pu L, Maicas G, Tian Y, Yamamura T, Nakamura M, Suzuki H, et al. Computer-aided diagnosis for characterisation of colorectal lesions: a comprehensive software including serrated lesions. Gastrointest Endosc. 2020.

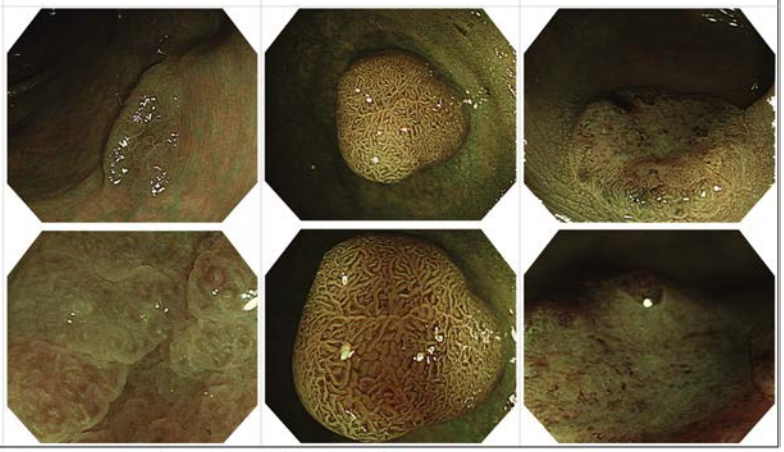
23. Ang TL, Li JW, Wong YJ, Tan Y-LJ, Fock KM, Tan MTK, et al. A prospective randomized study of colonoscopy using blue laser imaging and white light imaging in detection and differentiation of colonic polyps. Endoscopy International Open. 2019;07(10):E1207-E13.

7.4 Supplementary material for Chapter 7

	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	· Invisible *1	· Regular caliber · Regular distribution (meshed/spiral pattern) *2	· Variable caliber · Irregular distribution	· Loose vessel areas · Interruption of thick vessels
Surface pattern	· Regular dark or white spots · Similar to surrounding normal mucosa	· Regular (tubular/branched/papillary)	· Irregular or obscure	· Amorphous areas
Most likely histology	Hyperplastic polyp/ Sessile serrated polyp	Low grade intramucosal neoplasia	High grade intramucosal neoplasia/ Shallow submucosal invasive cancer *3	Deep submucosal invasive cancer
Endoscopic image				

Supplementary figure 1 - JNET classification

NBI International Colorectal Endoscopic (NICE) Classification*

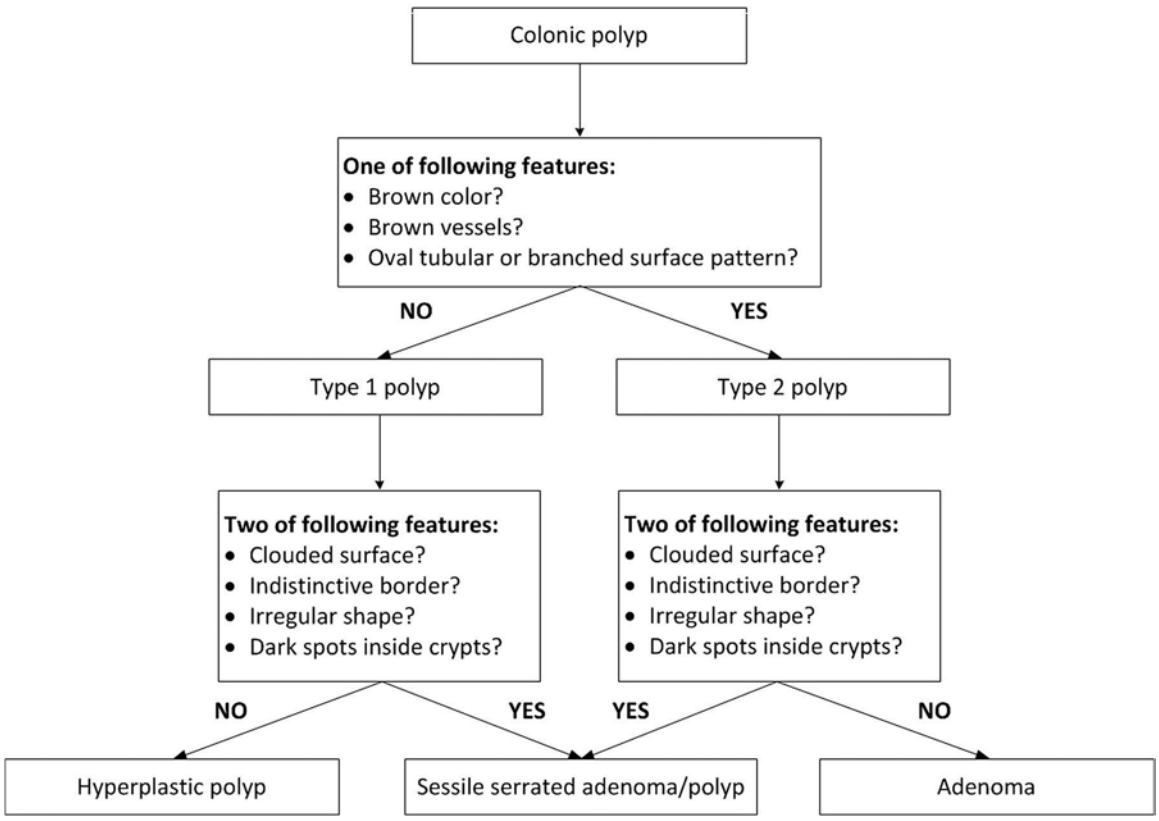
	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels coursing across the lesion	Brown vessels surrounding white structures**	Has area(s) of disrupted or missing vessels
Surface Pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structure surrounded by brown vessels**	Amorphous or absent surface pattern
Most likely pathology	**Hyperplastic**	**Adenoma*** **	**Deep submucosal invasive cancer**
Examples			

* Can be applied using colonoscopes with or without optical (zoom) magnification

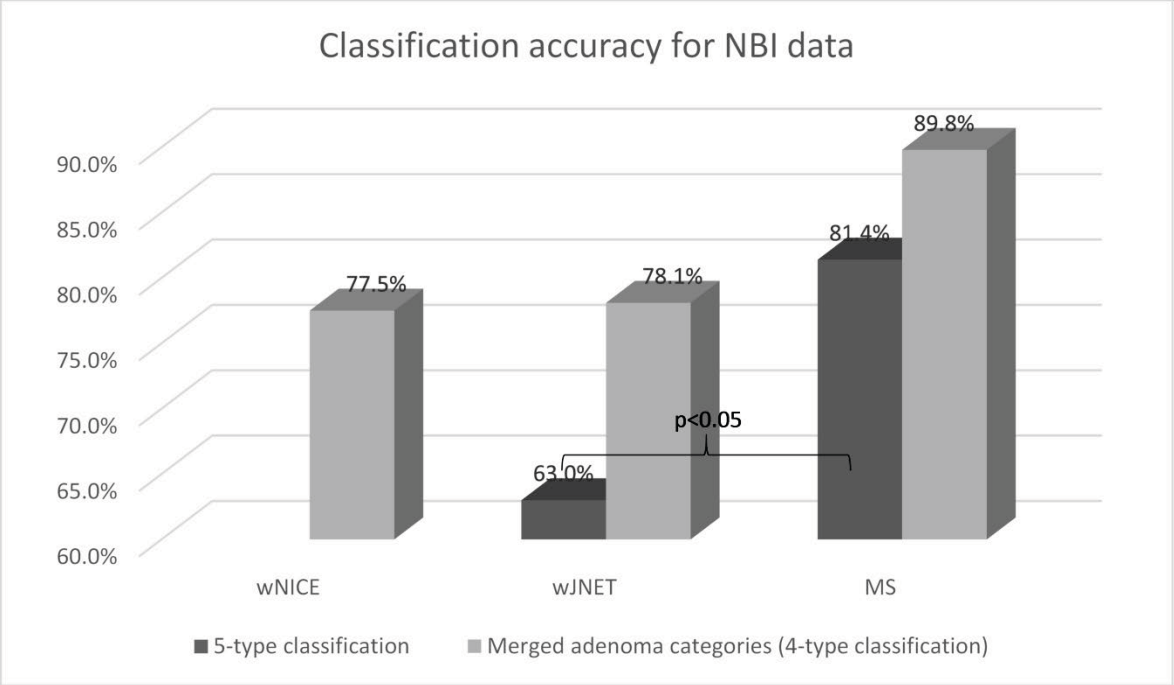
** These structures (regular or irregular) may represent the pits and the epithelium of the crypt opening.

*** Type 2 consists of Vienna classification types 3, 4 and superficial 5 (all adenomas with either low or high grade dysplasia, or with superficial submucosal carcinoma). The presence of high grade dysplasia or superficial submucosal carcinoma may be suggested by an irregular vessel or surface pattern, and is often associated with atypical morphology (e.g., depressed area).

Supplementary figure 2 - NICE classification



Supplementary figure 3 - WASP classification



Supplementary figure 4 – Accuracy for NBI subset with high confidence (validation phase)

Supplementary Table 1 - Diagnoses per histology according to wNICE classification (exploratory phase)

	High-confidence diagnosis Classification type (predicted histology)	Histology								
		HP	Inflammatory	SSA/P up to LGD	TA LGD	TVA or VA LGD	TSA LGD	SSA/P HGD	Adenoma HGD/ Superficial cancer	Invasive cancer
wNICE classification	wNICE 1 (HP)	33	0	14	4	0	0	0	0	0
	wNICE 1 (SSA/P up to LGD)	9	0	61	2	0	0	0	0	0
	wNICE 2 (SSA/P up to LGD)	2	0	1	0	0	0	0	0	0
	wNICE 2 (adenoma/HGD/superficial cancer)	11	4	3	228	61	1	2	28	3
	wNICE 3 (invasive cancer)	0	0	0	0	0	0	0	0	8

Legend

Severe misdiagnosis

Moderate misdiagnosis

Accurate diagnosis

HP – Hyperplastic polyp
SSA/P – Sessile serrated adenoma/polyp
TA – Tubular adenoma
TVA – Tubulovillous adenoma
VA – Villous adenoma
TSA – Traditional serrated adenoma
LGD – Low grade dysplasia
HGD – High grade dysplasia

Supplementary table 2 - Diagnoses per histology according to wJNET classification (exploratory phase)

	High-confidence diagnosis Classification type (predicted histology)	Histology								
		HP	Inflammatory	SSA/P up to LGD	TA LGD	TVA or VA LGD	TSA LGD	SSA/P HGD	Adenoma HGD/ Superficial cancer	Invasive cancer
wJNET classification	wJNET 1 (HP)	33	0	14	4	0	0	0	0	0
	wJNET 1 (SSA/P up to LGD)	9	0	61	2	0	0	0	0	0
	wJNET 2A (SSA/P up to LGD)	2	0	1	0	0	0	0	0	0
	wJNET 2A (adenoma LGD)	11	4	3	222	26	0	1	4	0
	wJNET 2B (adenoma/HGD/superficial cancer)	0	0	0	6	35	1	1	24	3
	wNICE 3 (invasive cancer)	0	0	0	0	0	0	0	0	8

Legend

Severe misdiagnosis

Moderate misdiagnosis

Accurate diagnosis

HP – Hyperplastic polyp
SSA/P – Sessile serrated adenoma/polyp
TA – Tubular adenoma
TVA – Tubulovillous adenoma
VA – Villous adenoma
TSA – Traditional serrated adenoma
LGD – Low grade dysplasia
HGD – High grade dysplasia

Supplementary Table 3 - Diagnoses per histology according to MS classification (exploratory phase)

	High-confidence diagnosis Classification type (predicted histology)	Histology								
		HP	Inflammatory	SSA/P up to LGD	TA LGD	TVA or VA LGD	TSA LGD	SSA/P HGD	Adenoma HGD/ Superficial cancer	Invasive cancer
MS classification	MS I (HP)	22	0	3	4	0	0	0	0	0
	MS IIo (SSA/P up to LGD)	10	0	64	2	0	0	0	0	0
	MS II (TA LGD)	10	2	4	221	11	0	0	4	0
	MS IIIa (TVA/VA/HGD/superficial cancer)	1	2	0	10	50	1	2	24	3

Legend

Severe misdiagnosis

Moderate misdiagnosis

Accurate diagnosis

HP – Hyperplastic polyp
SSA/P – Sessile serrated adenoma/polyp
TA – Tubular adenoma
TVA – Tubulovillous adenoma
VA – Villous adenoma
TSA – Traditional serrated adenoma
LGD – Low grade dysplasia
HGD – High grade dysplasia

Supplementary table 4 - High-confidence diagnoses per type and histology according to wNICE classification at validation phase

	High confidence diagnosis Classification type (predicted histology)	Histology								
		HP	Inflammatory	SSA/P up to LGD	TA LGD	TVA or VA LGD	TSA LGD	SSA/P HGD	Adenoma HGD/ Superficial cancer	Invasive cancer
wNICE classification	wNICE 1 (HP)	19	0	8	1	0	0	0	0	1
	wNICE 1 (SSA/P up to LGD)	5	0	15	0	1	0	0	0	0
	wNICE 2 (SSA/P up to LGD)	0	0	0	1	0	0	0	0	0
	wNICE 2 (adenoma/HGD/superficial cancer)	0	0	0	23	6	0	3	12	2
	wNICE 3 (invasive cancer)	0	0	0	0	0	0	0	4	10

Legend

Severe misdiagnosis

Moderate misdiagnosis

Accurate diagnosis

HP – Hyperplastic polyp
SSA/P – Sessile serrated adenoma/polyp
TA – Tubular adenoma
TVA – Tubulovillous adenoma
VA – Villous adenoma
TSA – Traditional serrated adenoma
LGD – Low grade dysplasia
HGD – High grade dysplasia

Supplementary table 5 - High-confidence diagnoses per type and histology according to wJNET classification at validation phase

	High confidence diagnosis Classification type (predicted histology)	Histology								
		HP	Inflammatory	SSA/P up to LGD	TA LGD	TVA or VA LGD	TSA LGD	SSA/P HGD	Adenoma HGD/ Superficial cancer	Invasive cancer
wJNET classification	wJNET 1 (HP)	19	0	8	1	0	0	0	0	1
	wJNET 1 (SSA/P up to LGD)	5	0	15	0	2	0	0	0	0
	wJNET 2A (SSA/P up to LGD)	0	0	0	0	0	0	0	0	0
	wJNET 2A (adenoma LGD)	0	0	0	20	4	0	1	10	0
	wJNET 2B (adenoma/HGD/superficial cancer)	0	0	0	3	1	0	2	6	3
	wNICE 3 (invasive cancer)	0	0	0	0	0	0	0	0	10

Legend

Severe misdiagnosis

Moderate misdiagnosis

Accurate diagnosis

HP – Hyperplastic polyp
SSA/P – Sessile serrated adenoma/polyp
TA – Tubular adenoma
TVA – Tubulovillous adenoma
VA – Villous adenoma
TSA – Traditional serrated adenoma
LGD – Low grade dysplasia
HGD – High grade dysplasia

Supplementary table 6 - High-confidence diagnoses per type and histology according to MS classification at validation phase

	High confidence diagnosis Classification type (predicted histology)	Histology								
		HP	Inflammatory	SSA/P up to LGD	TA LGD	TVA or VA LGD	TSA LGD	SSA/P HGD	Adenoma HGD/ Superficial cancer	Invasive cancer
MS classification	MS I (HP)	11	0	0	0	0	0	0	0	0
	MS IIo (SSA/P up to LGD)	3	0	23	0	2	0	0	0	1
	MS II (TA LGD)	0	0	0	17	1	0	0	0	0
	MS IIIa (TVA/VA/HGD/superficial cancer)	0	0	0	4	3	0	2	12	2
	MS IIIb (invasive cancer)	0	0	0	0	0	0	0	1	9

Legend

Severe misdiagnosis

Moderate misdiagnosis

Accurate diagnosis

HP – Hyperplastic polyp
SSA/P – Sessile serrated adenoma/polyp
TA – Tubular adenoma
TVA – Tubulovillous adenoma
VA – Villous adenoma
TSA – Traditional serrated adenoma
LGD – Low grade dysplasia
HGD – High grade dysplasia

Chapter 8

Computer-aided diagnosis for detection and characterization of colorectal lesions: comprehensive software including serrated lesions

This chapter offers a brief summary of a paper published in *Gastrointestinal Endoscopy*. The statement of authorship and a copy of the paper 'Computer-aided diagnosis for detection and characterisation of colorectal lesions: A comprehensive software including serrated lesions' follow over the page.

8.1 Summary

Even after studying which are the most accurate and comprehensive classifications up to date, the adequate use of such classifications falls back to each individual endoscopist. This means adequate training and continuous development are important in order to achieve satisfactory results. This might be more easily achievable in academic and expert centres compared to community hospitals and rural areas. A possible way to overcome this impasse is to lend an expert eye or opinion to less trained endoscopists. This has been traditionally sought through in locum courses and proctorship where experts would go to non-academic centres to help with training. However, this strategy is highly dependable of scarce human resources and has an inheritable high cost involved. Alternatively, an expert eye could also be lent through computer aided diagnosis systems, a form of AI based on deep learning that has been recently introduced for medical imaging and that can assist the endoscopist in histology prediction of colorectal lesions. In this study, we have developed and tested a CAD system based on the MS classification with both NBI and BLI imaging technologies.

The exploratory phase involved developing the CAD system, which was modelled with NBI colorectal lesion images from our endoscopy unit at the Lyell McEwin Hospital. Once the CAD had 'learnt' with the Australian dataset, it was initially tested with a separate dataset from Australia also on NBI. Then, the same CAD was tested on NBI and BLI datasets from Japan. For both learning and testing processes, the gold standard was always the histology report. The Australian dataset consisted of 1,235 polyp images on NBI, and the Japanese datasets consisted of 69 polyp images (20 on NBI and 49 on BLI). Our CAD software achieved a mean AUC of 94.3% when tested with the Australian dataset; a mean AUC of 84.5% when tested with the Japanese NBI dataset; and a mean AUC of 90.3% when tested with the Japanese BLI dataset.

Although still in its preliminary phases, these results are promising as they are comparable to what you would expect from an expert endoscopist. Further development of this software could enable an aide to every endoscopy room, improving diagnosis and hence treatment during colonoscopy.

8.2 Statement of authorship

Statement of Authorship

Title of Paper	Computer-aided diagnosis for characterisation of colorectal lesions: comprehensive software including serrated lesions
Publication Status	☑ Published ☐ Accepted for Publication ☒ ~~Submitted for Publication~~ ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Published in the Gastrointestinal Endoscopy journal Elsevier – ISSN: 0016-5107

Principal Author

Name of Principal Author (Candidate)	Leonardo Zorron Cheng Tao Pu		
Contribution to the Paper	Conceptualised and designed the study. Involved in data collection (exploratory and validation phases) and pre-processing (annotation). Interpreted the results and prepared the manuscript.		
Overall percentage (%)	60%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper		
Signature		Date	11/12/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Conceptualised and designed the study. Participated in data interpretation and critical revision of the manuscript for important intellectual content.		
Signature		Date	02/01/2020

ORIGINAL ARTICLE

Computer-aided diagnosis for characterization of colorectal lesions: comprehensive software that includes differentiation of serrated lesions

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Background and Aims: Endoscopy guidelines recommend adhering to policies such as resect and discard only if the optical biopsy is accurate. However, accuracy in predicting histology can vary greatly. Computer-aided diagnosis (CAD) for characterization of colorectal lesions may help with this issue. In this study, CAD software developed at the University of Adelaide (Australia) that includes serrated polyp differentiation was validated with Japanese images on narrow-band imaging (NBI) and blue-laser imaging (BLI).

Methods: CAD software developed using machine learning and densely connected convolutional neural networks was modeled with NBI colorectal lesion images (Olympus 190 series - Australia) and validated for NBI (Olympus 290 series) and BLI (Fujifilm 700 series) with Japanese datasets. All images were correlated with histology according to the modified Sano classification. The CAD software was trained with Australian NBI images and tested with separate sets of images from Australia (NBI) and Japan (NBI and BLI).

Results: An Australian dataset of 1235 polyp images was used as training, testing, and internal validation sets. A Japanese dataset of 20 polyp images on NBI and 49 polyp images on BLI was used as external validation sets. The CAD software had a mean area under the curve (AUC) of 94.3% for the internal set and 84.5% and 90.3% for the external sets (NBI and BLI, respectively).

Conclusions: The CAD achieved AUCs comparable with experts and similar results with NBI and BLI. Accurate CAD prediction was achievable, even when the predicted endoscopy imaging technology was not part of the training set. (Gastrointest Endosc 2020;■:1-9.)

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; AUC, area under the curve; BLI, blue-laser imaging; CAD, computer-aided diagnosis; CI, confidence interval; CNN, convolutional neural network; CRC, colorectal cancer; HP, hyperplastic polyp; MS, modified Sano; NBI, narrow-band imaging; SSA/P, sessile serrated adenoma/polyp; WASP, Workgroup on Serrated Polyps and Polyposis.

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INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy in the world, and its burden is expected to increase by 60% by 2030 to more than 2.2 million new cases and 1.1 million cancer deaths.[1] CRC incidence and mortality are increasing in rapidly transitioning countries with sizable populations, including Russia, China, and Brazil.[1] CRC represents a major health and economic burden on the health care systems of countries across the globe.[2] Screening programs involving fecal occult blood tests, flexible sigmoidoscopies, and colonoscopies have been introduced in various parts of the world to reduce this burden. It is estimated that over 1 million colonoscopies will be performed in Australia in 2020.[3]

During colonoscopy, polyp characterization is usually performed after polyp detection. The use of optical biopsy to predict the histology of colorectal lesions in vivo and in real-time during colonoscopy has been proposed to potentially improve cost-effectiveness in 4 main ways: (1) by reducing the need for histopathologic assessment after resecting precancerous polyps with small risk of an invasive component (eg, diminutive adenomas on optical biopsy); (2) by avoiding resection of benign polyps; (3) by determining the most appropriate resection method in real-time; and (4) by enabling a proposal for a follow-up period by the end of the procedure, avoiding a follow-up consult for this sole purpose. In line with the use of optical biopsy in clinical practice, the American Society for Gastrointestinal Endoscopy (ASGE) has recommended 2 strategies when dealing with diminutive colorectal polyps $\leq$5 mm: (1) resect and discard strategy for suspected cancerous lesions circumventing the need for histopathologic assessment, and (2) diagnose and leave strategy for suspected rectosigmoid hyperplastic polyps (HPs).[4] ASGE recommends that the resect and discard strategy can be adopted when the optical diagnosis provides $\geq$90% agreement for postpolypectomy surveillance intervals compared with the pathologic assessment. For the diagnose and leave strategy, the recommended negative predictive value is $\geq$90% for adenomatous histology. These are the criterion standard benchmarks for any optical biopsy method used to characterize GI lesions.[5]

However, the predictive accuracy of endoscopic imaging does not always reach these criterion standard benchmarks. In a prospective study of 527 polyps, Sharma et al[6] found that the overall predictive accuracy of all colorectal polyps was 45% using solely white-light imaging in most cases. Even though the use of virtual chromoendoscopy, such as narrow-band imaging (NBI), is expected to increase accuracy in predicting the histology of colorectal lesions, the variability among endoscopists is wide. The multicenter DISCARD 2 study carried out in 6 general hospitals confirmed that even for NBI, the accuracy of optical imaging was below the recommended ASGE standards, and thus optical imaging could not be recommended for routine clinical practice.[7] Another study found that only 3 of the 12 gastroenterologists evaluated after receiving training were able to achieve satisfactory results with real-time optical biopsy.[8]

Computer-aided diagnosis (CAD) uses the advances in artificial intelligence to offer a promising avenue to accurately characterize colorectal lesions in vivo and in real-time. More importantly, it could theoretically make an accurate prediction regardless of which center or endoscopist uses it. Although it is unclear how different endoscopic imaging technologies would interact with the CAD, it is expected that the CAD would perform similarly within the same type of endoscope on which it was trained (eg, NBI) if other cofactors are maintained (eg, bowel cleanliness). To the best of our knowledge, the development of an endoscopy CAD model for lesion characterization trained with one imaging technology and tested on a different technology is unheard of.

CAD systems for the characterization of images must have a choice of output or result. The more specific the results it gives, the less accurate the system will be. Therefore, the use of final histology as output (eg, tubular adenoma with low-grade dysplasia) would likely make the system too inaccurate. On the other hand, the use of overly simplified classification systems (eg, dichotomy of benign and malignant polyps) might impair the capability of clinical decision making. Hence, most CADs for characterization of colorectal lesions to date have used clinically relevant groupings such as the NBI international colorectal endoscopic (NICE) classification[9] and the Sano classification.[10]

Most endoscopic classifications lack the ability to differentiate precancerous sessile serrated adenoma/polyps (SSA/Ps) from benign HPs. To date, only 2 NBI classification systems have this capability: the modified Sano (MS) classification and the Workgroup on Serrated Polyps and Polyposis (WASP) add-on classification.[11,12] Although both MS and WASP (when added to standard classifications such as NICE) could potentially be used as output for a CAD, recent studies have shown the potential of better results with MS compared with NICE and the Japanese NBI Expert Team classification, even when combined with WASP.[13,14]

The aim of our study was to develop CAD software using a deep convolutional neural network (CNN) model based on NBI to differentiate colorectal lesions into 5 subtypes according to the MS classification.[11,13] In addition, the performance of the CAD was tested with colorectal lesions from another center on both NBI and blue-laser imaging (BLI). The MS classification was chosen because it is currently the only NBI-based standalone classification to include adenoma and serrated polyp differentiation. Because the serrated pathway is known to be a major contributor to CRC alongside the adenoma pathway, the ability to differentiate neoplastic and non-neoplastic serrated lesions was deemed necessary for a comprehensive CAD.

METHODS

For the exploratory phase, an image database of images of colorectal lesions from adult patients who underwent elective colonoscopies at a tertiary hospital in South

Australia was assessed retrospectively (January 2010 to December 2016). The use of images collected retrospectively was authorized by the Human Research and Ethics Committee (reference number 283), and individual consent was waived. Furthermore, from January 2017 to June 2018, images of colorectal lesions were retrieved prospectively. The prospective collection of images was also approved by the Human and Research Ethics Committee (reference number 2008128) and required individual consent. As an eligibility criterion for the retrospectively collected images, these had to be acquired with Olympus 190 HQ series (Exera III; Center Valley, Pa, USA) colonoscopes. All images included in the prospective exploratory phase were taken by an Olympus 190 HQ series (Exera III) colonoscope. Eligible retrospective and prospective procedures were performed by an expert in advanced endoscopic imaging (R.S.). For the prospective images, patients less than 18 years of age, those undergoing emergency colonoscopy, pregnant women, those with total colectomy, a previous diagnosis of inflammatory bowel disease, familial adenomatous polyposis syndrome or Peutz-Jeghers syndrome were excluded before signing the consent form. Those unwilling to participate in the study were also excluded. Patients with no colorectal lesions identified or who had any endoscopic signs of inflammatory bowel disease during the colonoscopy were excluded after consenting to the study. Patients who could not have a colonoscopy completed to the most proximal part of the colon (eg, poor bowel preparation leading to rescheduling, Boston Bowel Preparation Scale <6, or those with acute angulations) were excluded.

All images selected for the exploratory phase were clear and magnified (near focus) NBI images. CAD software was then developed based on this dataset (ie, Australian dataset) using a densely connected CNN.[15] The learning steps included data augmentation in the form of preprocessing (ie, random rotation, horizontal and vertical flips, and random-centered crops). The model was evaluated using 5-fold cross-validation with the Australian dataset. In this process, the dataset was divided into 5 parts, with 80% used for training and 20% for testing. For each fold, we trained the model with an Adam optimizer[16] with a learning rate of 0.00001 for 75 epochs and a batch size of 32. The splits followed the same class distribution as that of the entire Australian dataset (ie, MS I = 8%; MS II = 35%; MS IIo = 24%; MS IIIa = 24%; MS IIIb = 9%). The performance of the model was then assessed through the mean area under the receiver operational characteristic curve (AUC) and 95% confidence interval (CI) across the 5 folds. These 5 models were then run for testing with both Japanese datasets (NBI and BLI), and the mean AUC and 95% CI of the 5 runs were computed.

The validation phase was carried with a partner institution (Nagoya, Japan). The Japanese dataset consisted of 2 subsets retrieved from a tertiary hospital image database: magnified NBI images acquired with the Olympus 290 series; and magnified BLI images acquired with the Fujifilm 700 series (Phoenix, Ariz, USA). All images were correlated with histology and uniquely de-identified into folders according to the MS classification.[11,13] To determine the area of interest within each image, software for polyp annotation was used by an endoscopist experienced in advanced imaging and colonoscopy (L.Z.C.T.P.) (Fig. 1). The design of the study is summarized in a flowchart (Fig. 2). All images were clustered by patient; hence, images from the same patient were never used in both training and testing sets. The final experiments for both the exploratory and validation phases were run on November 18, 2019.

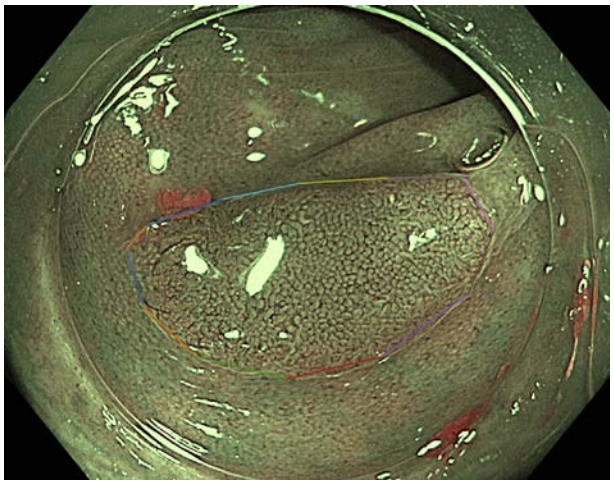

Figure 1. Example of the delineation process for manually determining the area of interest.

The primary outcome was the development and accuracy assessment of a CAD based on the NBI Australian dataset through the AUC. Due to the unbalanced dataset (ie, higher number of precancerous lesions compared with HPs), sample-based accuracy would bias the results toward classes with more samples. The AUC was then used as an option to provide an unbiased classification performance. Secondary outcomes included the accuracy evaluation of the CAD trained with the Australian dataset and tested with the Japanese dataset (both with NBI and BLI). The chi-squared test was used to compare 2 AUCs with their respective standard errors. Standard errors were calculated from the 95% CIs using the following formula: standard error = (upper limit − lower limit)/3.92. The 95% CIs were estimated according to Hanley and McNeil[17] SAS 9.4 statistical software (SAS Institute Inc, Cary, NC) was used.

This study was approved by the Nagoya University Hospital Ethics Review Committee (2015-0485) and the Human Research Ethics Committee (TQEH/LMH/MH) under the reference numbers HREC/16/TQEH/283 and 2008128. This committee is constituted in accordance with the NHMRC National Statement on Ethical Conduct in Human Research (2007) and incorporating all updates.

RESULTS

In the exploratory phase, the Australian dataset included 1235 images of colorectal lesions correlated to the

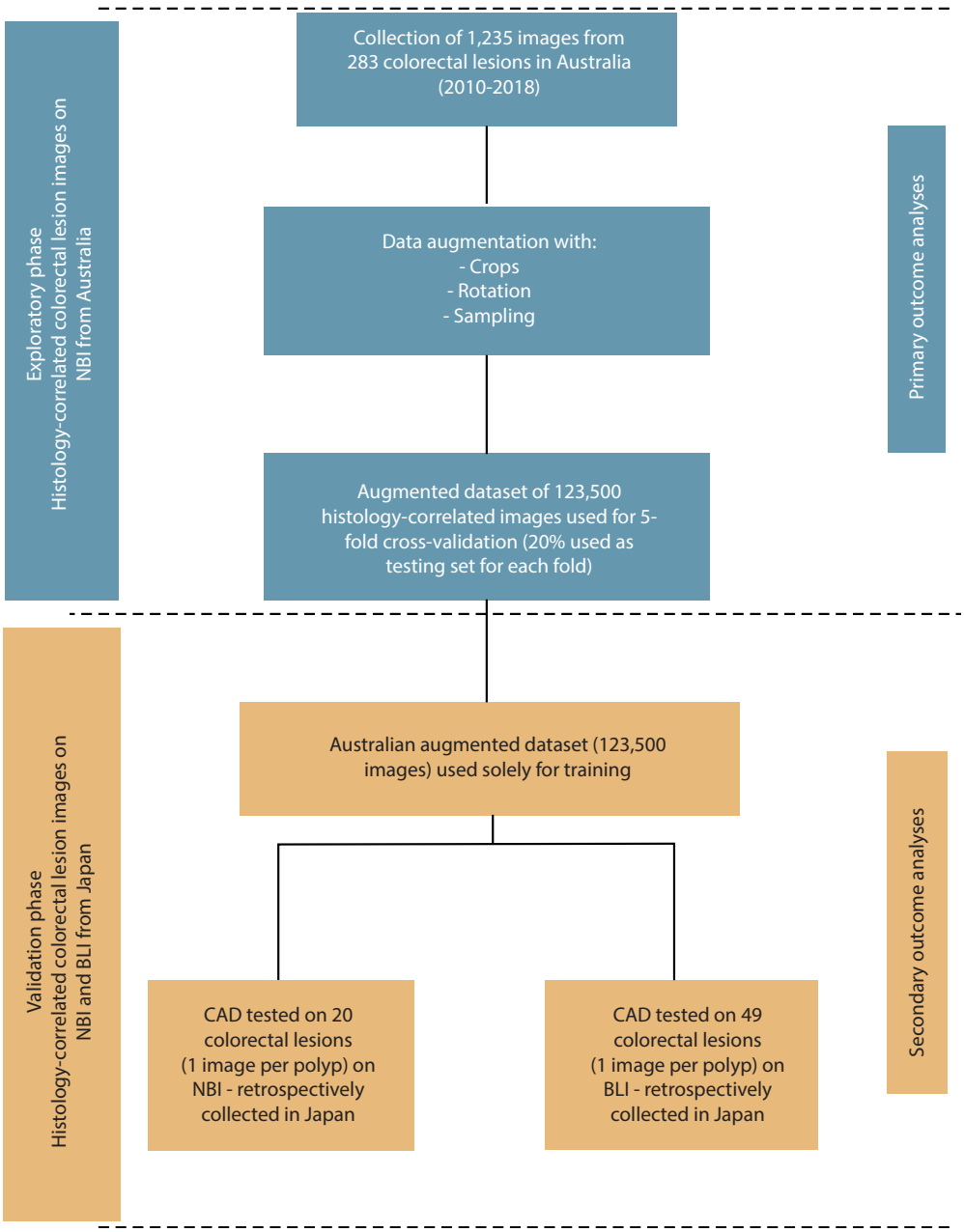

Figure 2. Study flowchart.

following histology: 103 HPs (MS I); 429 low-grade tubular adenomas (MS II); 293 nondysplastic or low-grade SSA/Ps (MS IIo); 295 tubulovillous adenomas or villous adenomas or any high-grade colorectal lesion (MS IIIa); and 115 invasive colorectal cancers (MS IIIb). All classes were used for both training and validation. One of 5 folds was used for evaluation at each cross-validation iteration (247 colorectal lesion images used on average, ranging from 230 to 263, for the 5 validation processes). The mean AUC for the 5-fold validation varied from 93.3% to 96.2%, achieving an average AUC of 94.3%. Results for the exploratory phase 5-fold cross-validation process were computed class by class by AUC and then averaged over the classes (Fig. 3). The confusion matrix of the average results for the 5-fold cross-validation process based on the 5-class classification for the exploratory phase is also presented (Fig. 4).

For the validation phase, the Japanese datasets consisting of 20 colorectal lesions on NBI (3 MS I, 5 MS II, 2 MS IIo, 7 MS IIIa, and 3 MS IIIb) and 49 colorectal lesions on BLI (9 MS I, 10 MS II, 10 MS IIo, 11 MS IIIa, and 9 MS IIIb) were used. For the Japanese dataset, only 1 image per lesion was used; and for the Australian dataset an average of 4 images per lesion (from different angles) were used. The CAD software achieved a mean AUC of 84.5% (range, 78.3% to 88.6%) and 90.3% (range, 87.9% to 92.8%) for the NBI and BLI Japanese validation datasets

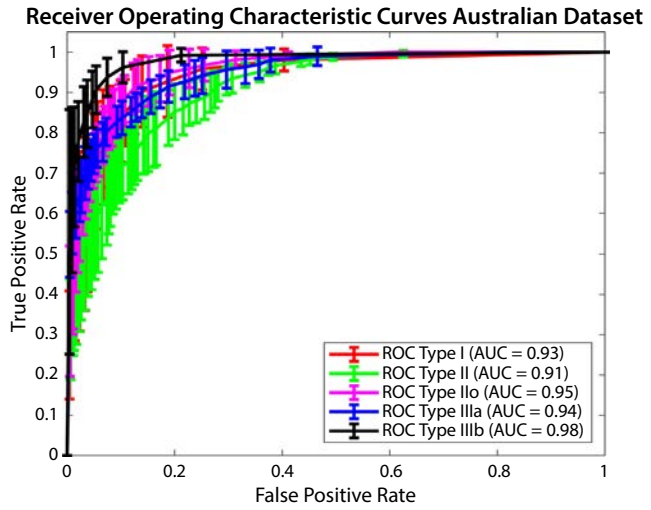

Figure 3. Mean receiver operating characteristic (ROC) curves (AUC) and 95% confidence intervals per class for the exploratory phase (Australian dataset).

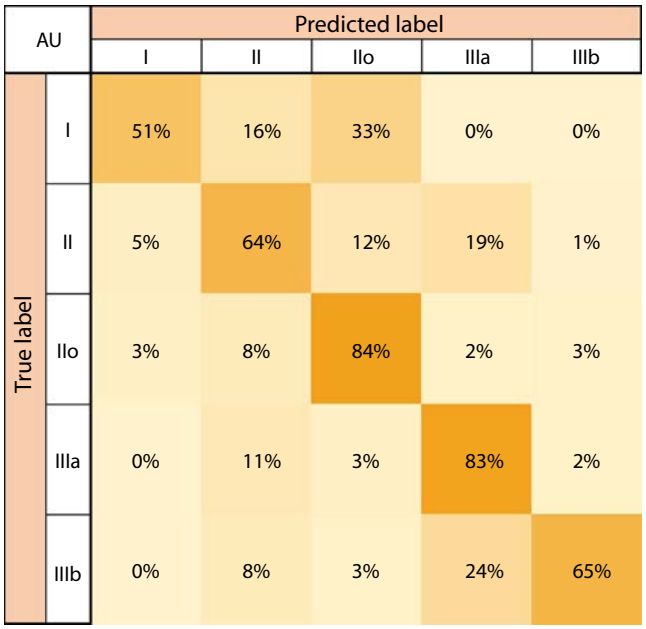

Figure 4. Confusion matrix representing the average diagnoses per class throughout the 5-fold cross-validation process (exploratory phase). *AU*, Australian dataset.

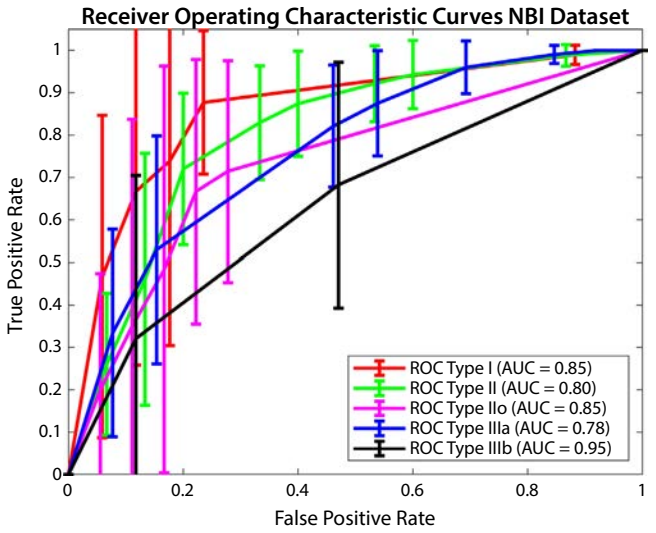

Figure 5. Mean receiver operating characteristic (ROC) curves (AUC) per class for the validation phase (narrow-band imaging).

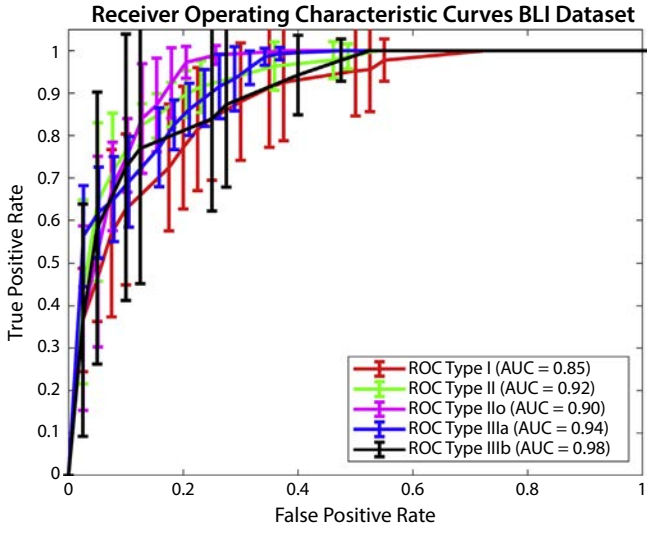

Figure 6. Mean receiver operating characteristic (ROC) curves (AUC) per class for the validation phase (blue-laser imaging).

(Figs. 5 and 6), respectively. Average AUCs per class with 95% confidence intervals and comparisons per class between datasets are provided in Table 1. The mean AUCs between the exploratory and validation phases (for NBI and BLI) and within the validation phase were similar (ie, cannot reject the null hypothesis, $P > .05$). The distribution of predicted and actual histology according to the MS classification are displayed as confusion matrices in Figures 7 and 8 for the Japanese NBI and BLI datasets, respectively. After training, our model provided real-time output (processing time was at least 30 images/second).

DISCUSSION

In the past few years, several CAD models for colorectal lesions have been developed around the world. Initially, support vector machine models were used, which required manual designing of features to enable characterization of images.[18,19] However, deep learning approaches, such as CNNs, have produced more accurate image classification results than traditional machine learning methods[20] and have enabled automated design of features. More recent CADs developed for characterizing colorectal lesions have used deep learning-based CNN models. However, they lack the ability to predict SSA/Ps.[10,21,22] Differentiation of SSA/Ps from HPs is important because serrated polyps account for

TABLE 1. Pairwise comparisons of AUC class by class among the Australian, Japanese NBI, and Japanese BLI datasets

Comparison	First AUC value	First standard error	Second AUC value	Second standard error	Chi-squared	*P* value
AU(I) vs JP_NBI(I)	0.93460	0.01577	0.85098	0.14411	0.3327	.5641
AU(I) vs JP_BLI(I)	0.93460	0.01577	0.85333	0.07763	1.0526	.3049
JP_NBI(I) vs JP_BLI(I)	0.85098	0.14411	0.85333	0.07763	0.0002	.9885
AU(II) vs JP_NBI(II)	0.90846	0.00982	0.79733	0.12878	0.7404	.3895
AU(II) vs JP_BLI(II)	0.90846	0.00982	0.91949	0.06008	0.0328	.8563
JP_NBI(II) vs JP_BLI(II)	0.79733	0.12878	0.91949	0.06008	0.7390	.3900
AU(IIo) vs JP_NBI(IIo)	0.95082	0.00860	0.85000	0.21365	0.2223	.6373
AU(IIo) vs JP_BLI(IIo)	0.95082	0.00860	0.92051	0.05645	0.2816	.5956
JP_NBI(IIo) vs JP_BLI(IIo)	0.85000	0.21365	0.92051	0.05645	0.1018	.7497
AU(IIIa) vs JP_NBI(IIIa)	0.94327	0.00923	0.77582	0.12066	1.9145	.1665
AU(IIIa) vs JP_BLI(IIIa)	0.94327	0.00923	0.90431	0.05921	0.4228	.5155
JP_NBI(IIIa) vs JP_BLI(IIIa)	0.77582	0.12066	0.90431	0.05921	0.9138	.3391
AU(IIIb) vs JP_NBI(IIIb)	0.97674	0.00898	0.95294	0.18732	0.0161	.8990
AU(IIIb) vs JP_BLI(IIIb)	0.97674	0.00898	0.91778	0.07115	0.6760	.4110
JP_NBI(IIIb) vs JP_BLI(IIIb)	0.95294	0.18732	0.91778	0.07115	0.0308	.8607

AUC, Area under the curve; *NBI*, narrow-band imaging; *BLI*, blue-laser imaging; *AU*, Australian dataset; *JP_NBI*, Japanese NBI dataset; *JP_BLI*, Japanese BLI dataset.

15% to 30% of all CRCs.[23,24] As SSA/Ps are often confused with HPs by endoscopists,[6] this contributes to interval CRC.[25] Up-to-date CAD models have differentiated the polyps into only 2 subtypes[18,19,22,26] or 3 subtypes.[10,27,28] Our CAD was conceived based on the MS classification and hence has the ability to differentiate polyps into 5 categories, including the differentiation of SSA/Ps. A CAD capable of characterizing as benign only HPs as opposed to any serrated polyps would be the safest for use in clinical practice.

Our mean AUC for NBI prediction in the range of 93% to 96% is consistent with the accuracy measures found in previous trials with experts using the MS classification. The studies describe an AUC of 92% and overall accuracy of 97%, respectively.[11,13] It is common for experts to have higher diagnostic performance than nonexperts, therefore we expect that our results would be better if compared with nonexpert performance. For instance, although not statistically significant, the AUC of experts with a 4-type classification was numerically higher compared with that of nonexperts.[29]

As with any innovative technology, the use of CAD for characterization of colorectal lesions should be used at first in combination with human (endoscopist) judgment. Hence, we propose that a deductive reasoning process could be used for a combined diagnosis. This would allow combined decisions to be made when the endoscopist and CAD agree on the predicted histology or when the endoscopist and CAD disagree on the predicted histology. An example of the first scenario would be when the endoscopist believes a large lesion is an SSA/P but is not confident. However, with the CAD corroborating this, the endoscopist could become more comfortable about proceeding with endoscopic resection of the lesion. When the endoscopist and CAD disagree on the diagnosis, it could also be helpful. For instance, if the CAD defines a lesion as neoplastic but the endoscopist believes it is non-neoplastic, instead of taking no action, the endoscopist would then proceed with biopsy or resection. As our CAD processing time for output is almost immediate, computer-assisted intervention would be feasible.

The CAD system outlined in this study was designed to provide the diagnosis on a single frame and hence is supposed to provide its output once the endoscopist freezes the image on the lesion with magnified NBI. Therefore, the characterization of large lesions is a challenge. Different portions of a large lesion might present with different histology, one more reason for the CAD to be used in conjunction with an experienced endoscopist. The correct selection of the area to be sampled when freezing the frame would undoubtably have an impact on the lesion's prediction.

Making CAD software such as this available in the form of a downloadable application is an exciting possibility. Our group is currently looking this into in a follow-up study. This would allow ease of access and subsequently aid endoscopists in making accurate diagnoses during colonoscopy. However, to be able to do that, the CAD must be capable of working across the different colonoscopes available. The validation phase of this study has demonstrated that this is achievable. Similar results to the exploratory phase were found when the CAD was tested against different colonoscopes with the same imaging technology (ie, Olympus 190 and 290 series); and against different technologies (ie, NBI and BLI). The fact that although similar, the results were numerically higher for the

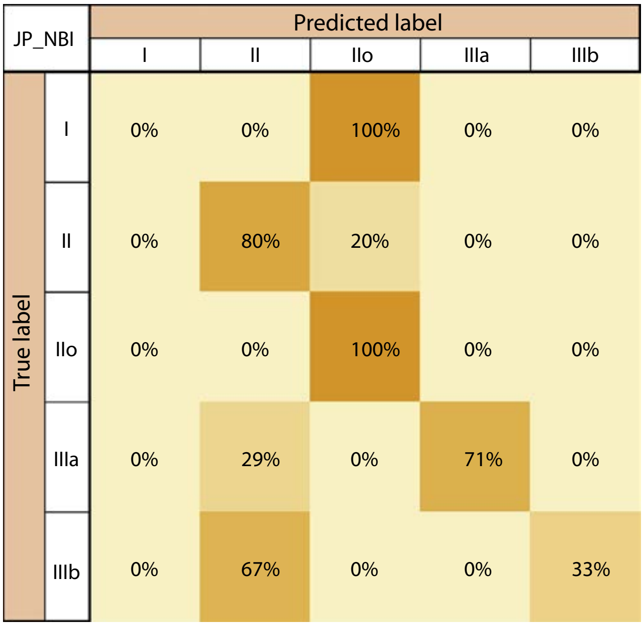

Figure 7. Confusion matrix representing the average diagnoses per class throughout the 5-fold cross-validation process (validation phase, narrow-band imaging). *JP_NBI*, Japanese narrow-band imaging dataset.

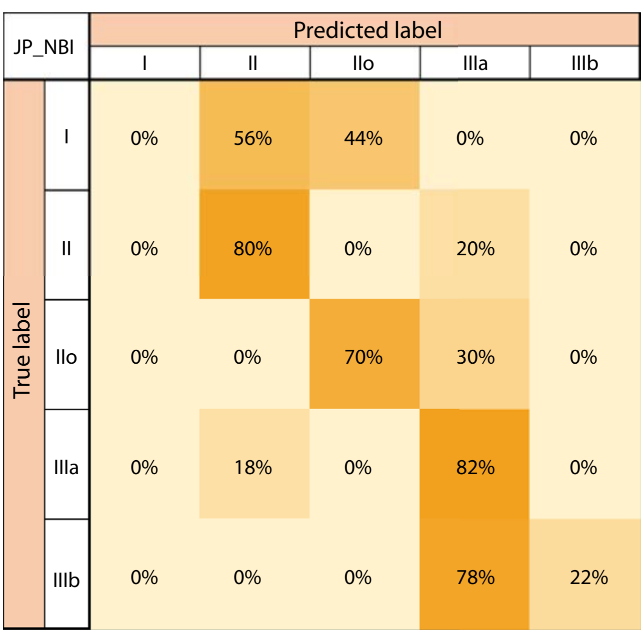

Figure 8. Confusion matrix representing the average diagnoses per class throughout the 5-fold cross-validation process (validation phase, blue-laser imaging). *JP_BLI*, Japanese blue-laser imaging dataset.

Japanese BLI dataset compared with the Japanese NBI dataset might be due to the small size of the Japanese NBI dataset (ie, 20 colorectal lesions) or the type of magnification used. For both the Australian and Japanese BLI datasets, the magnification was standardized (push-up button for the Olympus 190 and Fujifilm 760); whereas for the Japanese NBI dataset the magnification was done by a lever (Olympus 290). Despite these limitations, the strategy of a downloadable CAD may help with its own self-improvement if a feedback system could be incorporated within the software. This would allow the software to keep learning and, as a consequence, improve the CAD's accuracy over time for all systems.

A limitation of the study is a relatively small training set. Initially, we identified the need for a large training set when the numbers provided by our initial retrospective collection of data were shown to be insufficient for achieving good results. Although the period for screening eligible images was over 5 years, only images acquired from mid-2012 onward used the 190 series colonoscope. Therefore, the retrospective training set of approximately 800 images had to be complemented by prospective collection of images. Although a larger training set than what we currently have could theoretically provide a better AUC, our current AUC is already similar to that found for experts. This, along with the possibility of continuous improvement with a potential feedback system, and the possibility of pre-training and fine-tuning allowed by CNN models, are likely to address the relatively small training set.

The current CAD model has predicted most neoplastic lesions as neoplastic but has also predicted a considerable number of benign lesions as neoplastic. Although this is not ideal, removing a benign lesion is preferable to not removing a neoplastic one. It is expected that with further development of the software, through a more complex model and/or a larger training set, the false positives would be reduced.

Our CAD system currently does not have an integrated detection process, hence an endoscopist is required to select the area of interest within each image. This is currently being researched within our group, and it should be possible to make the CAD fully automated for characterization of endoscopic images of colorectal lesions in the near future. In addition, our system lacks a high-confidence category for its diagnosis. This is thought to be implemented based on the threshold for selecting the appropriate class. The current design selects the appropriate class as the one with highest probability (eg, chooses class I if the likeliness results are I = 40%, II = 20%, IIo = 20%, IIIa = 15%, IIIb = 5%). Although our approach still needs to be tested, we believe that a minimum threshold of 50% probability could be a good choice for high-confidence diagnoses.

The validation phase was set at another center with different colonoscopes for assessment of the breadth of reproducibility as a proof of concept. Assessment of a CAD for characterization with training and testing based on different imaging technologies is unheard of; therefore, we decided to perform a pilot with a limited number of

images to evaluate the feasibility of such an approach. As a result, the current validation phase had small numbers and did not cover all possible colonoscopy imaging technologies. However, such limitations were partially addressed because the 2 major virtual chromoendoscopic imaging technologies were evaluated (ie, NBI and BLI), and all experiments were performed 5 times; the average results are presented in this article. Therefore, our small dataset shows how our CAD training methodology behaves for previously unseen datasets, highlighting good domain adaptation capabilities. Nevertheless, future studies with larger numbers in the validation set are warranted to confirm our findings.

Although it is not possible to assert that our CAD would be useful widely, to the best of our knowledge this is the first study where a CAD for characterization has been developed based on one type of image for the training set and validated with different colonoscopes and imaging technologies. Therefore, the promising results found with our small validation dataset suggest that it will be possible to have a CAD trained mostly with one technology and used with another technology. Strategies that could be used to improve the results for other devices involve inclusion of a small parcel of images from the other technology into the training set and enlargement of the validation datasets.

In conclusion, the CAD software achieved AUCs as good as experts and similar across 2 different imaging technologies (NBI and BLI). An accurate CAD prediction was achievable even when the predicted endoscopy imaging technology was not part of the training set.

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REFERENCES

1. Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017;66:683-91.
2. Pyenson B, Pickhardt PJ, Sawhney TG, et al. Medicare cost of colorectal cancer screening: CT colonography vs. optical colonoscopy. Abdom Imaging 2015;40:2966-76.
3. Bowel Cancer Australia. A Colonoscopy Wait-time and Performance Guarantee. Available at: https://www.bowelcanceraustralia.org/early-detection/a-colonoscopy-wait-time-and-performance-guarantee. Accessed November 18, 2019.
4. Rex DK, Kahi C, O'Brien M, et al. The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on real-time endoscopic assessment of the histology of diminutive colorectal polyps. Gastrointest Endosc 2011;73:419-22.
5. Abu Dayyeh BK, Thosani N, Konda V, et al. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting real-time endoscopic assessment of the histology of diminutive colorectal polyps. Gastrointest Endosc 2015;81: 502.e1-16.
6. Sharma P, Frye J, Frizelle F. Accuracy of visual prediction of pathology of colorectal polyps: how accurate are we? ANZ J Surg 2014;84: 365-70.
7. Rees CJ, Rajasekhar PT, Wilson A, et al. Narrow band imaging optical diagnosis of small colorectal polyps in routine clinical practice: the Detect Inspect Characterise Resect and Discard 2 (DISCARD 2) study. Gut 2017;66:887-95.
8. Ladabaum U, Fioritto A, Mitani A, et al. Real-time optical biopsy of colon polyps with narrow band imaging in community practice does not yet meet key thresholds for clinical decisions. Gastroenterology 2013;144:81-91.
9. Byrne MF, Chapados N, Soudan F, et al. Real-time differentiation of adenomatous and hyperplastic diminutive colorectal polyps during analysis of unaltered videos of standard colonoscopy using a deep learning model. Gut 2019;68:94-100.
10. Tamai N, Saito Y, Sakamoto T, et al. Effectiveness of computer-aided diagnosis of colorectal lesions using novel software for magnifying narrow-band imaging: a pilot study. Endosc Int Open 2017;5:E690-4.
11. Singh R, Jayanna M, Navadgi S, et al. Narrow-band imaging with dual focus magnification in differentiating colorectal neoplasia. Dig Endosc 2013;25(Suppl 2):16-20.
12. IJspeert JE, Bastiaansen BA, van Leerdam ME, et al. Development and validation of the WASP classification system for optical diagnosis of adenomas, hyperplastic polyps and sessile serrated adenomas/polyps. Gut 2016;65:963-70.
13. Zorron Cheng Tao Pu L, Cheong KL, Koay DSC, et al. Randomised controlled trial comparing modified Sano's and narrow band imaging international colorectal endoscopic classifications for colorectal lesions. World J Gastrointest Endosc 2018;10: 210-8.
14. Zorron Cheng Tao Pu L, Yamamura T, Nakamura M, et al. Modified Sano's is the most accurate classification for characterising serrated polyps and adenomas with different virtual chromoendoscopy methods: results of a prospective study. J Gastroenterol Hepatol 2019;34(Suppl 2):226-7.
15. Huang G, Liu Z, Van Der Maaten L, et al. Densely connected convolutional networks. In Proceedings of the IEEE conference on computer vision and pattern recognition 2017; pp. 4700-8.
16. Kingma DP, Ba J. Adam: a method for stochastic optimization. International Conference on Learning Representations. Available at: https://arxiv.org/abs/1412.6980.
17. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143: 29-36.
18. Takemura Y, Yoshida S, Tanaka S, et al. Computer-aided system for predicting the histology of colorectal tumors by using narrow-band imaging magnifying colonoscopy (with video). Gastrointest Endosc 2012;75: 179-85.
19. Kominami Y, Yoshida S, Tanaka S, et al. Computer-aided diagnosis of colorectal polyp histology by using a real-time image recognition system and narrow-band imaging magnifying colonoscopy. Gastrointest Endosc 2016;83:643-9.
20. Krizhevsky A, Sutskever I, Hinton GE. ImageNet classification with deep convolutional neural networks. Commun ACM 2017;60: 84-90.
21. Ribeiro E, Uhl A, Wimmer G, et al. Exploring deep learning and transfer learning for colonic polyp classification. Comput Math Methods Med 2016;2016:6584725.
22. Chen PJ, Lin MC, Lai MJ, et al. Accurate classification of diminutive colorectal polyps using computer-aided analysis. Gastroenterology 2018;154:568-75.
23. Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. Histopathology 2007;50: 113-30.

24. Samowitz WS, Albertsen H, Herrick J, et al. Evaluation of a large, population-based sample supports a CpG island methylator phenotype in colon cancer. Gastroenterology 2005;129:837-45.
25. Kahi CJ, Hewett DG, Norton DL, et al. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. Clin Gastroenterol Hepatol 2011;9:42-6.
26. Stefanescu D, Streba C, Cartana ET, et al. Computer aided diagnosis for confocal laser endomicroscopy in advanced colorectal adenocarcinoma. PLoS One 2016;11:e0154863.
27. Mesejo P, Pizarro D, Abergel A, et al. Computer-aided classification of gastrointestinal lesions in regular colonoscopy. IEEE Trans Med Imaging 2016;35:2051-63.
28. Misawa M, Kudo SE, Mori Y, et al. Accuracy of computer-aided diagnosis based on narrow-band imaging endocytoscopy for diagnosing colorectal lesions: comparison with experts. Int J Comput Assist Radiol Surg 2017;12:757-66.
29. Sano Y, Tanaka S, Kudo S-e, et al. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. Dig Endosc 2016;28:526-33.

Chapter 9

Microbiota profile is different for early and invasive colorectal cancer and is consistent throughout the colon

This chapter offers a brief summary of a paper published in the *Journal of Gastroenterology and Hepatology*. The statement of authorship and paper (.pdf) 'Microbiota profile is markedly different for early and invasive colorectal cancer; and is consistent throughout the colon' follow over the page.

9.1 Summary

In addition to endoscopic imaging, other factors can help the endoscopist when deciding what the predicted histology of the colorectal lesion is. Some examples are location (e.g. traditional serrated adenomas are more common in the rectosigmoid region) and previous history of a certain type of polyp (e.g. in the serrated polyposis syndrome). However, other forms of identification might also be possible. As specific bacteria within the gut microbiome (i.e. Fusobacterium genus) have been shown to have an increased relative abundance in CRC patients, in this study we have evaluated if and which bacteria can be used for differentiation of invasive and superficial cancer lesions/patients.

In this study, patients referred to the endoscopy department of Nagoya University Hospital with either superficial or invasive CRC were assessed. Samples were taken from stool pre-bowel preparation and from the mucosal mucus through endoscopic brushes during the colonoscopy. DNA extraction, 16S rRNA next generation sequencing and biostatistics were then performed for determining the microbiota present in each group. The primary focus was to determine the difference in relative abundance of the Fusobacterium genus between the groups. The 14 patients with invasive cancer have shown a higher relative abundance of Fusobacterium compared to the 11 patients with early cancer. In addition, 5 other bacteria genera were found to be increased and 4 decreased in invasive CRC patients.

These results need to be further confirmed by larger studies, but potentially could lead to diagnostic and therapeutic roles of these microbiota in the setting of early CRC.

9.2 Statement of authorship

Statement of Authorship

Title of Paper	Microbiota profile is different for early and invasive colorectal cancer; and is consistent throughout the colon
Publication Status	☑ Published ~~☑ Accepted for Publication~~ ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	~~Accepted for publication~~ Published in the Journal of Gastroenterology and Hepatology (Online ISSN: 1440-1746)

Principal Author

Name of Principal Author (Candidate)	Leonardo Zorron Cheng Tao Pu		
Contribution to the Paper	Conceptualised and designed the study. Participated in data collection and DNA extraction, biostatistics and interpretation of results. Drafted the manuscript.		
Overall percentage (%)	60		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	15/09/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Kenta Yamamoto		
Contribution to the Paper	Participated in conceptualisation, DNA extraction, biostatistics, interpretation of results and manuscript edits.		
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GASTROENTEROLOGY

Microbiota profile is different for early and invasive colorectal cancer and is consistent throughout the colon

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Key words
colonoscopy, colorectal neoplasms, *Fusobacterium nucleatum*, gastrointestinal microbiome, microbiota.

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Abstract

Background and Aim: Microbiota have been associated with several diseases including colorectal cancer (CRC). This study aimed to evaluate the microbiota in early/invasive CRC utilizing stool and cytological brushes to determine differences in relative abundance (RA).

Methods: Colonoscopy patients referred for endoscopic submucosal dissection or previous to CRC surgery were prospectively enrolled. Stool was collected pre-bowel preparation; and brush samples were taken during colonoscopy (three regions). DNA extraction, 16S rRNA next generation sequencing, and biostatistics (QIIME and STAMP software packages) followed. Primary outcome was the difference in RA of the *Fusobacterium* genus between the groups. Secondary outcomes included analyses of other microbiota.

Results: Twenty-five patients were included, of which 14 had invasive cancer (≥ 1000 mm into the submucosa). The three major genera for invasive cancer were *Bacterioides*, *Oribacterium*, and *Fusobacterium*, whereas for early cancer were *Oribacterium, Bacterioides*, and *Prevotella* (decreasing order of RA). There was a significantly higher RA of *Fusobacterium* in the invasive cancer group (9.65% *vs* 0.95%, respectively, $P < 0.001$). The RA of all genera was similar throughout the colon. In addition to *Fusobacterium*, the genera *Corynebacterium, Enterococcus, Neisseria, Porphyromonas*, and *Sclegelella* showed statistically higher RA in the invasive cancer group. Conversely, the genera *Oribacterium, Desulfovibrio, Clostridiales*, and *Lactobacillus* showed lower RA in the invasive cancer group.

Conclusions: The RA of *Fusobacterium* is higher with invasive CRC than in early CRC patients. In addition, five other bacteria genera were found to be increased, and four decreased in invasive CRC patients. The microbiota per patient was similar throughout the colon.

Introduction

The interaction of humans with microbiota has become the focus of interest in a wide range of medical research. The gut microbiota specifically has been demonstrated to be associated with numerous conditions, including colorectal cancer (CRC).[1]

In the past few years, several studies have found evidence that a specific gram-negative anaerobic bacterium was consistently associated with CRC: the *Fusobacterium nucleatum* (Fn). This species has been shown to have an increased relative abundance (RA) in patients with CRC in many different cohorts.[2,3] The question whether Fn plays a role in CRC carcinogenesis or if it is only a marker for CRC is still under debate. Some studies advocate it is solely a marker as it has only been associated with CRC as opposed to advanced adenomas.[4,5] However, other studies have found an apparent correlation of Fn abundance with increasing grades of dysplasia within the adenoma–adenocarcinoma pathway, possibly through the stimulation of inflammatory mediators.[6,7] Although some studies have included high-grade dysplastic lesions, microbiota mostly have been extracted from human tissue. This is not ideal as bacteria mostly stay in the mucous covering the gastrointestinal tract.

Fusobacterium nucleatum has been initially studied within periodontal health and its presence in the oral mucosa biofilm. It has been shown that the influence of Fn as either a mutualist or pathogenic microbe relies on its interactions with other microbiota within the biofilm.[8] Although some CRC microbiota studies have studied the presence of Fn among dysplastic adenomatous lesions, the microbiota has been extracted from either fecal samples or human tissue biopsies. The diminutive proportion of biofilm in these samples might have undermined the results as it is expected that most Fn would be found in the mucous cap/biofilm rather than in the tissue or fecal material. Therefore, although the use of stool

is more practical, the use of brush cytology theoretically would provide more accurate information on mucosal surface microbiota in the gut.

This study intends to evaluate the microbiota within the biofilm of early and invasive CRC patients utilizing cytological brushes and stool samples to determine the differences in RA of Fn.

Methods

Patients undergoing colonoscopy in 2018 at Nagoya University Hospital either for endoscopic submucosal dissection (ESD) or previous to a CRC surgery were prospectively enrolled. This study has been approved by the Ethics Review Committee from Nagoya University Hospital, and all patients enrolled have been consented. Stool samples were taken pre-bowel preparation in two circumstances: (i) When the patient took his/her bowel preparation at home, he/she would collect the sample him/herself 1 day prior to taking the bowel preparation and store it in a commercially prepared plastic container with guanine as preservation liquid (©2018 Techno Suruga Laboratory Co.,Ltd., Shizuoka, Japan) in the refrigerator until the colonoscopy. This kit allows DNA quality for 16S rRNA sequencing similar to −80°C storage.[9] (ii) When the patient took his/her bowel preparation as inpatient, the ward nurses collected the sample and stored in a commercially prepared plastic container (©2018 Techno Suruga Laboratory Co., Ltd., Shizuoka, Japan) without any preservation liquid at −15°C for a short period of time.

The samples taken during colonoscopy utilized the cytological brush (G22108-CCB-7-240-3-S from ©2018 Cook Medical). Each sample utilized one brush, which had the tip cut-off into a 2-mL Eppendorf Safe-Lock microcentrifuge tube containing 650 μL of buffer solution provided by the DNA extraction kit. All samples were collected prior any endoscopic procedure took place (e.g. biopsy, tattoo, and ESD). The brush samples were collected from three different regions: (i) caecum opposite to the ileocaecal valve, (ii) normal mucosa near the lesion (i.e. two folds distal to the lesion), and (iii) the lesion itself. If the lesion was located less than 10 cm from the anal verge, the "normal mucosa" sample was then collected twofolds proximal to the lesion.

All brush samples had their DNA extracted on the same day of the sample collection with the QIAmp UCP Pathogen Kit (©2018 QIAGEN, Hilden, Germany). The stool samples had their DNA extracted on the same day of the brush samples (less than 1 week from sampling) with the DNeasy PowerSoil Kit (©2018 QIAGEN, Hilden, Germany). After the DNA was extracted, all leftover samples and extracted DNA samples were immediately stored at −80° C. The library preparation was conducted according to the Illumina Miseq System guidelines for 16S rRNA next generation sequencing. The primers used were to target the V3–4 regions bacterial 16S rRNA regions (forward 5′-TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCACTCAGGGGGCGCAG-3; and reverse 5′-GTCTCGTGTGGCTCGGAGTCAGGAGTGTATAAGAGAGAGGACTACHVGGGTATCTAATCC-3).

Demographic data statistics was done using chi-squared test for comparison of proportions and Mann–Whitney *U*-test for comparison of means. Normality was assessed through the Shapiro–Wilk test. Biostatistics for Miseq results involved initial processing with the Quantitative Insights into Microbial Ecology (QIIME) 1.9.1 software package (including quality check, chimera filtering, and OTU assignment with the expanded Human Oral Microbiota Database).[10] USEACH 6.1 software[11] was used within QIIME to remove chimeric sequences. The results from QIIME were interpreted with the STAMP software package utilizing Welch's *t*-test for two group comparison and ANOVA for comparison of multiple groups, with two-sided 95% confidence interval and considered significant when $P \leq 0.05$. Primary outcome was the difference in RA of Fn between invasive and early cancer groups. Secondary outcomes consisted of describing the bacteria genera RA difference between the two groups. RA was defined as the evenness of distribution of individuals (species or genus) among its peers within the studied community (i.e. collected samples). The distribution of the gut microbiome was expected to follow a normal distribution as per previous trials.

Results

Twenty-six patients were initially invited to participate because a clinical–endoscopic diagnosis of early or invasive cancer. One patient was excluded after enrolment because of the pathology result (low-grade dysplastic adenoma). Twenty-five patients were included in the final analysis. Fifteen underwent an initial ESD procedure, and 10 were sent directly to surgery. From the ESD group, four were found to have invasion into the submucosa > 1000 mm after resection, and three were subsequently sent to salvage surgery (after multidisciplinary and patient/family discussion, a T1b cancer patient has decided to be followed up). Although no difference in gender between the groups, statistically significant differences regarding age, location of tumor, and Paris classification were found (Table 1). The three major genera in the invasive cancer group (n = 14) were *Bacterioides*, *Oribacterium*, and *Fusobacterium*,

Table 1 Cohort demographics

		Early cancer (n = 11)	Invasive cancer (n = 14)	P value
	Age - mean (IQR)	66 (13)	72.6 (5.8)	0.13
	Male - n (%)	5 (45.5)	6 (42.9)	0.90
Location n (%)	Caecum	2 (18.2)	0 (0)	0.10
	Ascending colon	3 (27.3)	1 (7.1)	0.18
	Transverse colon	3 (27.3)	2 (14.3)	0.43
	Descending colon	0 (0)	1 (7.1)	0.38
	Sigmoid colon	0 (0)	6 (42.9)	0.01
	Rectum	3 (27.3)	4 (28.6)	0.94
Paris classification n (%)	0-IIa	7 (63.6)	0 (0)	<0.01
	0-IIa + 0-Is	4 (36.4)	4 (28.6)	0.68
Borrmann classification n (%)	type I	-	1 (7.1)	-
	type II	-	9 (64.3)	-
Histology n (%)	Tis	10 (90.9)	-	-
	T1a	1 (9.4)	-	-
	T1b	-	4 (28.6)	-
	T2	-	5 (35.7)	-
	T3	-	3 (21.4)	-

IQR – Interquartile range.

whereas the three major genera in the early cancer group ($n = 11$) were *Oribacterium*, *Bacterioides*, and *Prevotella* (in decreasing order of RA). There was a significantly higher RA of *Fusobacterium* in invasive cancer group compared with the superficial cancer group (9.65% vs. 0.95%, $P < 0.0001$, Fig. 1). This difference between invasive and early cancer groups was also significant when analyzing solely the 15 patients submitted to ESD (i.e. all those with endoscopic appearance of early cancer - $P = 0.02$).

The RA of all genera was similar throughout the colon. The RA of the *Fusobacterium* genus showed a similar difference between groups not only within the colon (10.4% versus 1.0%, $P < .0001$) but also for stool samples (7.3% versus 0.7%, $P = 0.05$). In addition to *Fusobacterium*, the genera *Corynebacterium*, *Enterococcus*, *Neisseria*, *Porphyromonas* and *Sclegelella* showed statistically significant higher RA in the invasive cancer group. Conversely, the genera *Oribacterium*, *Desulfovibrio*, *Clostridiales* and *Lactobacillus* showed a lower RA in the invasive cancer group for colon samples. Detailed information on all genera detected to be significantly different between groups for either sampling method has been summarized in supporting information table S1. Further interrogation of the above-mentioned genera at species level allowed to identify a statistically significant difference regarding *Oribacterium parvum* and *Clostridiales* [F-1][G-2] *bacterium* (lower in the invasive cancer group, $P < 0.01$ for both species) – Figures 2 and 3.

Looking into the specific *Fusobacterium* species, a statistically significant higher RA was found for *Fusobacterium* HMT 203 (6.56% versus 0.6%, $P = 0.001$) and for *Fusobacterium nucleatum* subspecies *vicentii* (0.04% versus $2x10^{-4}$%, $P = 0.04$), between invasive cancer and early cancer groups, respectively. This difference was significant also when looking into the brush samples only (Figs. 4, and 5).

Discussion

The association of microbiota with the adenoma-adenocarcinoma pathway has been the subject in several recent studies. Patients with invasive CRC have been consistently described with higher RA of Fusobacterium when compared to healthy controls.[3] However, differences in the RA of Fusobacterium and other microbiota between healthy controls and patients with adenomas is less consistent. There is evidence both for and against such differences.[4,6] In addition, a recent metanalysis has found that a different microbiota profile can be found between adenoma and CRC patients, including higher RA of Fusobacterium for CRC patients.[2] This supports our results of different gut microbiota associated with early and invasive CRC.

Our results have shown that most of the early CRC group had lesions in the proximal colon (8 out of 11) whilst most of the invasive cancer group had lesions in the distal colon (11 out of 14). This could lead to a potential bias as it has been reported that left colon CRC presents with higher Fusobacterium abundance compared to right colon CRC. However, even looking at specific subgroups (i.e. only proximal colon and only distal colon patients), invasive cancer group still presented with statistically significant higher RA of Fusobacterium ($P < 0.01$ and $P < 0.001$, respectively).

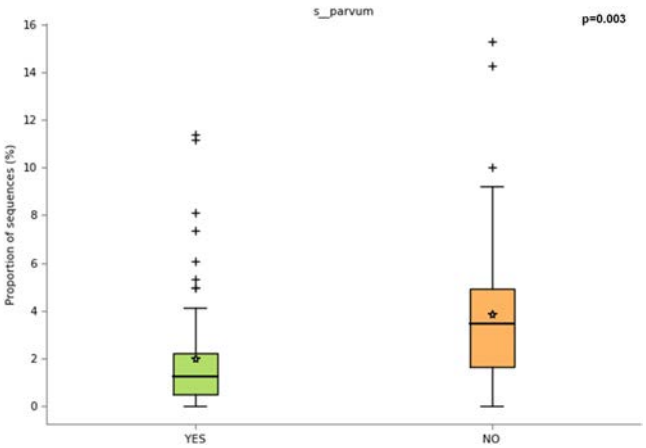

Figure 2 *Oribacterium parvum* profile for invasive (YES) and early (NO) colorectal cancer (colon samples).

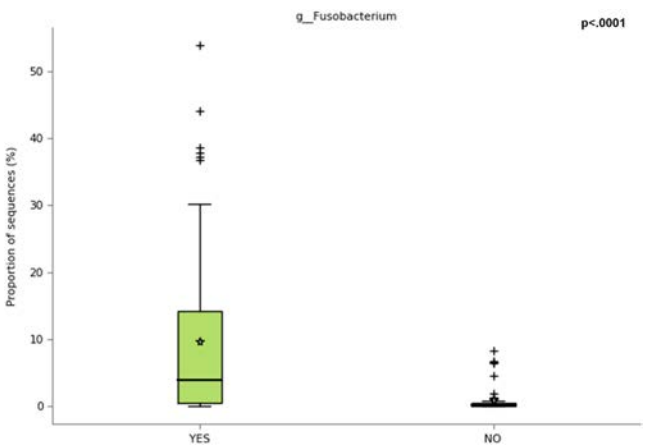

Figure 1 *Fusobacterium* genera profile for invasive (YES) and early (NO) colorectal cancer.

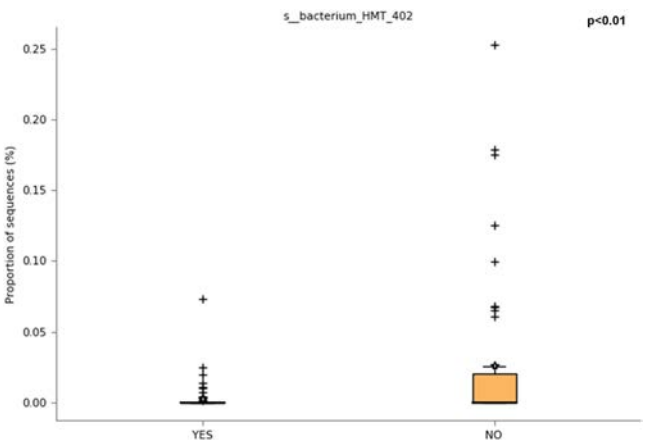

Figure 3 *Clostridiales bacterium* profile for invasive (YES) and early (NO) colorectal cancer (colon samples).

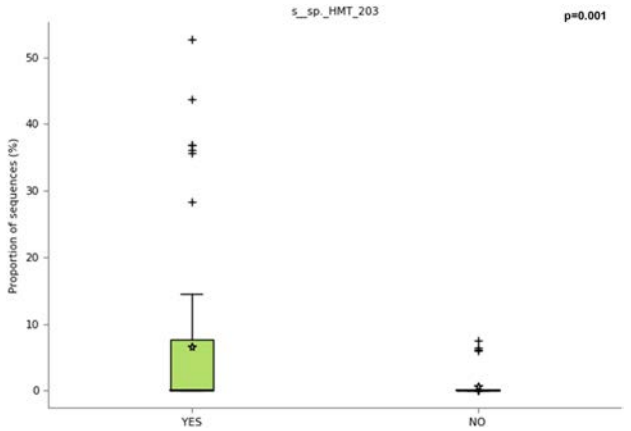

Figure 4 Fusobacterium HMT203 profile for invasive (YES) and early (NO) colorectal cancer (colon samples).

There is a range of uses for the microbiota in the CRC context. It involves the pre-malignant, early malignant and invasive CRCs' diagnosis,[2] prognosis[12] and potentially treatment.[13] Our findings allowed us to identify bacteria that are found both in higher and lower RA in invasive cancer patients compared to early cancer patients. The initial finding of significant higher *Fusobacterium* genus in both colon and feces gives support to the studies that used *Fusobacterium* fecal tests for CRC.[14,15] However, the p value for such difference in fecal samples differed greatly from the brush samples ($P = 0.05$ and $P < .0001$, respectively – Supporting information table S1). In addition, we could only isolate some difference in species when looking at colon samples. We hypothesize that although several *Fusobacteria* species are associated with the presence of neoplastic tissue what can be detected in stool, different species might be associated with invasiveness and might only be identifiable through colon samples (i.e. *nucleatum* subspecies *vicentii* and HMT 203). Therefore, on top of fecal tests for screening, there might be a role for identification of bacteria species *in situ* for prediction of invasiveness.

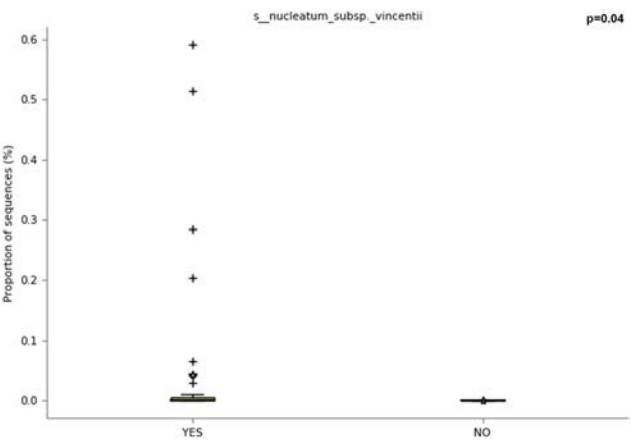

Figure 5 Fn *vicentii* profile for invasive (YES) and early (NO) colorectal cancer (colon samples).

The identification of specific species associated with invasive opposed to early cancer could further aid the troublesome prediction of early versus invasive cancer. A recent large prospective study has found an accuracy and sensitivity for deep invasion prediction of 77% and 58.4%, respectively.[16] The use of quantitative tests for RA of specific bacteria (e.g. Fn) in addition to endoscopic imaging could potentially improve this prediction. If such test could be developed to be used in real-time during colonoscopy, it would most likely aid in the prediction of invasion for potential endoscopically resectable colorectal lesions.

Finally, the identification of different bacteria associated even within the late stages of dysplasia supports that manipulation of the gut microbiota (e.g. through pre or probiotics) could have a role in the progression from early to invasive cancer. A possible postulation could be that the use of probiotics (e.g. *Lactobacillus*) from the moment a colorectal advanced lesion has been detected in a low-complexity endoscopy center could avoid progression. As the timespan from referred for ESD and the actual procedure can vary greatly, this simple action could slow its progression and increase the likelihood that the lesion is amenable for endoscopic resection when the time comes.

The limitations of the present study include the limited number of patients which could have negatively affected the number of bacteria identified to be statistically different between the groups. Nevertheless, the 10 bacteria genera (and 4 specific species) we have identified to be statistically different between early and invasive CRC could aid in future research.

In this research we have utilised the eHOMD database for OTU picking instead of most commonly used SILVA and Greengenes databases. As eHOMD is a more recent database and focused on where originally Fn was found (oral microbiota),[17] we understand that this would provide more accurate results for our main outcome.

In conclusion, the RA of Fn is higher in patients with invasive CRC than in early CRC patients; and is consistent throughout the colon. Other bacteria such as *Corynebacterium*, *Enterococcus*, *Neisseria*, *Porphyromonas* and *Sclegelella* were also found to be increased in invasive CRC. Conversely, the genera *Oribacterium*, *Desulfovibrio*, *Clostridiales* and *Lactobacillus* were found to be have lower RA in patients with invasive CRC. The microbiota pattern found per patient was not statistically different throughout the colon. The results of this study might potentially assist the endoscopist in determining if a lesion is endoscopically resectable and perhaps even provide insights into the treatment of these malignancies with pre or probiotic therapy.

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References

1 Murphy CL, O'Toole PW, Shanahan F. The gut microbiota in causation, detection, and treatment of cancer. *Am. J. Gastroenterol.* 2019; **114**: 1036–42.

2 Thomas AM, Manghi P, Asnicar F *et al*. Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation. *Nat. Med.* 2019; **25**: 667–78.
3 Dai Z, Coker OO, Nakatsu G *et al*. Multi-cohort analysis of colorectal cancer metagenome identified altered bacteria across populations and universal bacterial markers. *Microbiome.* 2018; **6**: 70.
4 Amitay EL, Werner S, Vital M *et al*. *Fusobacterium* and colorectal cancer: causal factor or passenger? Results from a large colorectal cancer screening study. *Carcinogenesis* 2017; **38**: 781–8.
5 Yoon H, Kim N, Park JH *et al*. Comparisons of gut microbiota among healthy control, patients with conventional adenoma, sessile serrated adenoma, and Colorectal Cancer. *J. Cancer Prev.* 2017; **22**: 108–14.
6 Rezasoltani S, Asadzadeh Aghdaei H, Dabiri H, Akhavan Sepahi A, Modarressi MH, Nazemalhosseini Mojarad E. The association between fecal microbiota and different types of colorectal polyp as precursors of colorectal cancer. *Microb. Pathog.* 2018; **124**: 244–9.
7 Proenca MA, Biselli JM, Succi M *et al*. Relationship between *Fusobacterium nucleatum*, inflammatory mediators and microRNAs in colorectal carcinogenesis. *World J. Gastroenterol.* 2018; **24**: 5351–65.
8 Brennan CA, Garrett WS. Fusobacterium nucleatum — symbiont, opportunist and oncobacterium. *Nat. Rev. Microbiol.* 2019; **17**: 156–66.
9 Nishimoto Y, Mizutani S, Nakajima T *et al*. High stability of faecal microbiome composition in guanidine thiocyanate solution at room temperature and robustness during colonoscopy. *Gut* 2016; **65**: 1574–5.
10 Escapa IF, Chen T, Huang Y, Gajare P, Dewhirst FE, Lemon KP. New insights into human nostril microbiome from the expanded human oral microbiome database (eHOMD): a resource for the microbiome of the human aerodigestive tract. *mSystems.* 2018; **3**: e00187–18.
11 Edgar RC. Search and clustering orders of magnitude faster than BLAST. *Bioinformatics (Oxford, England).* 2010; **26**: 2460–1.
12 Mima K, Nishihara R, Qian ZR *et al*. *Fusobacterium nucleatum* in colorectal carcinoma tissue and patient prognosis. *Gut* 2016; **65**: 1973–80.
13 Gorska A, Przystupski D, Niemczura MJ, Kulbacka J. Probiotic Bacteria: A Promising Tool in Cancer Prevention and Therapy. *Curr. Microbiol.* 2019; **76**: 939–49.
14 Suehiro Y, Sakai K, Nishioka M *et al*. Highly sensitive stool DNA testing of *Fusobacterium nucleatum* as a marker for detection of colorectal tumours in a Japanese population. *Ann. Clin. Biochem.* 2017; **54**: 86–91.
15 Wong SH, Kwong TNY, Chow TC *et al*. Quantitation of faecal *Fusobacterium* improves faecal immunochemical test in detecting advanced colorectal neoplasia. *Gut* 2017; **66**: 1441–8.
16 Puig I, Lopez-Ceron M, Arnau A *et al*. Accuracy of the narrow-band imaging international colorectal endoscopic classification system in identification of deep invasion in colorectal polyps. *Gastroenterology* 2019; **156**: 75–87.
17 Zheng W, Tsompana M, Ruscitto A *et al*. An accurate and efficient experimental approach for characterization of the complex oral microbiota. *Microbiome.* 2015; **3**: 48.

Supporting information

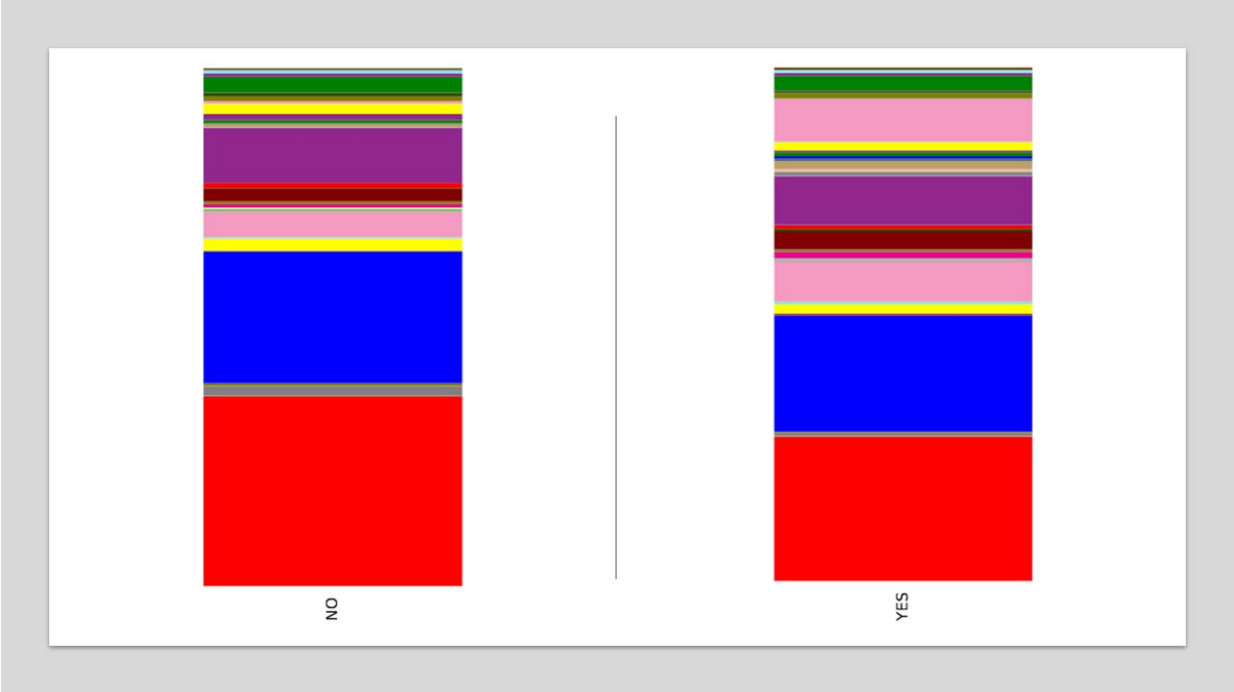
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Microbiota distribution for invasive and early CRC groups.

Table S1. Microbiota for invasive and early CRC groups analysed by type of sample.

Data S1. Supporting information.

9.4 Supplementary material for Chapter 9



Supporting information figure 1 – Microbiota distribution for invasive and early CRC groups

Colour	Phylum	Family	Genus	YES (invasive cancer)	NO (early cancer)
	Unassigned	Unassigned	Unassigned	28.0%	36.7%
	Bacteroidetes	Bacteroidaceae	Bacteroides	22.5%	25.5%
	Firmicutes	Lachnospiraceae_[XIV]	Oribacterium	9.5%	10.5%
	Bacteroidetes	Prevotellaceae	Prevotella	7.9%	5.1%
	Proteobacteria	Enterobacteriaceae	Other	2.9%	3.1%
	Fusobacteria	Fusobacteriaceae	Fusobacterium	8.3%	0.5%
	Firmicutes	Streptococcaceae	Streptococcus	1.2%	0.7%
	Firmicutes	Lachnospiraceae_[XIV]	Other	3.4%	2.5%
	Firmicutes	Veillonellaceae	Veillonella	1.6%	1.9%
	Bacteroidetes	Porphyromonadaceae	Tannerella	1.9%	2.4%

Legend for supporting information figure 1 – Top 10 microbiota

Supporting information table 1 – Microbiota for invasive and early CRC groups analysed by type of sample

Genus	**Sample type**	**Invasive cancer group RA - % (SD)**	**Early cancer group RA - % (SD)**	**p value**
Fusobacterium	All samples	9.65 (12.95)	0.95 (2.05)	p<.0001
	Colonic brush samples	10.43 (13.45)	1.05 (2.08)	p<.0001
	Faecal samples	7.32 (10.95)	0.67 (1.92)	p=0.05
Clostridiales_[F-1][G-2]	All samples	0.00 (0.01)	0.03 (0.06)	p<0.01
	Colonic brush samples	0.00 (0.00)	0.01 (0.04)	p=0.15
	Faecal samples	0.01 (0.02)	0.08 (0.08)	p<0.05
Schlegelella	All samples	1.33 (1.93)	0.55 (0.95)	p<0.01
	Colonic brush samples	1.33 (1.92)	0.56 (0.89)	p<0.05
	Faecal samples	1.33 (1.96)	0.51 (1.08)	p=0.21
Bacillaceae (family)[◊]	All samples	0.01 (0.02)	0.44 (1.11)	p<0.05
	Colonic brush samples	0.00 (0.01)	0.54 (1.26)	p<0.05
	Faecal samples	0.02 (0.03)	0.12 (0.28)	p=0.26
Anaerococcus	All samples	0.10 (0.30)	0.00 (0.00)	p<0.05
	Colonic brush samples	0.13 (0.34)	0.00 (0.00)	p<0.05
	Faecal samples	0.01 (0.03)	0.00 (0.00)	p=0.25
Peptidiphaga	All samples	0.00 (0.00)	0.00 (0.00)	p<0.05
	Colonic brush samples	0.00 (0.00)	0.00 (0.00)	p<0.05
	Faecal samples	0.00 (0.00)	0.00 (0.00)	p=0.36
Eikenella	All samples	0.01 (0.03)	0.00 (0.00)	p<0.05
	Colonic brush samples	0.01 (0.04)	0.00 (0.00)	p<0.05
	Faecal samples	0.00 (0.01)	0.00 (0.00)	p=0.29
Campylobacterales (order)[◊]	All samples	0.05 (0.15)	0.00 (0.01)	p<0.05
	Colonic brush samples	0.07 (0.18)	0.00 (0.02)	p<0.05
	Faecal samples	0.01 (0.02)	0.00 (0.00)	p=0.17
Peptoniphilus	All samples	0.08 (0.20)	0.01 (0.05)	p<0.05
	Colonic brush samples	0.09 (0.21)	0.02 (0.06)	p<0.05
	Faecal samples	0.04 (0.14)	0.00 (0.00)	p=0.33
Lactobacillus	All samples	0.02 (0.04)	0.06 (0.12)	p<0.05
	Colonic brush samples	0.01 (0.03)	0.05 (0.10)	p=0.08
	Faecal samples	0.03 (0.06)	0.12 (0.16)	p=0.15
Erysipelotrichaceae (family)[◊]	All samples	0.22 (0.50)	0.06 (0.13)	p<0.05
	Colonic brush samples	0.29 (0.55)	0.08 (0.15)	p<0.05
	Faecal samples	0.01 (0.01)	0.00 (0.01)	p=0.37
Oribacterium	All samples	12.34 (11.42)	17.42 (10.54)	p<0.05
	Colonic brush samples	14.51 (12.29)	21.19 (9.45)	p=0.01
	Faecal samples	5.85 (3.49)	6.13 (2.50)	p=0.82
Parvimonas	All samples	0.34 (0.99)	0.03 (0.09)	p<0.05
	Colonic brush samples	0.44 (1.13)	0.04 (0.10)	p<0.05
	Faecal samples	0.04 (0.06)	0.00 (0.00)	p=0.05
Corynebacterium	All samples	0.02 (0.04)	0.00 (0.01)	p<0.05
	Colonic brush samples	0.02 (0.04)	0.00 (0.01)	p<0.05
	Faecal samples	0.00 (0.01)	0.00 (0.01)	p=0.92
Solobacterium	All samples	0.00 (0.00)	0.00 (0.00)	p<0.05
	Colonic brush samples	0.00 (0.00)	0.00 (0.00)	p<0.05

	Faecal samples	0.00 (0.00)	0.00 (0.00)	p=1.00
Neisseria	All samples	0.30 (0.72)	0.08 (0.23)	p<0.05
	Colonic brush samples	0.40 (0.81)	0.10 (0.26)	p<0.05
	Faecal samples	0.00 (0.01)	0.00 (0.00)	p=0.18
Desulfovibrio	All samples	0.16 (0.23)	0.31 (0.44)	p<0.05
	Colonic brush samples	0.11 (0.16)	0.15 (0.19)	p=0.25
	Faecal samples	0.31 (0.33)	0.79 (0.61)	p<0.05
Granulicatella	All samples	0.87 (2.25)	0.23 (0.35)	p<0.05
	Colonic brush samples	1.16 (2.53)	0.30 (0.38)	p<0.05
	Faecal samples	0.01 (0.02)	0.02 (0.02)	p=0.75
Porphyromonas	All samples	0.36 (0.79)	0.12 (0.30)	p<0.05
	Colonic brush samples	0.38 (0.70)	0.16 (0.33)	p=0.08
	Faecal samples	0.30 (1.02)	0.01 (0.02)	p=0.31
Enterococcus	All samples	0.12 (0.28)	0.04 (0.08)	p<0.05
	Colonic brush samples	0.10 (0.24)	0.05 (0.09)	p=0.19
	Faecal samples	0.18 (0.38)	0.01 (0.03)	p=0.13
Finegoldia	All samples	0.05 (0.18)	0.00 (0.01)	p<0.05
	Colonic brush samples	0.07 (0.21)	0.00 (0.01)	p=0.06
	Faecal samples	0.01 (0.04)	0.00 (0.00)	p=0.34
Ruminococcaceae_[G-2]	All samples	0.08 (0.27)	0.00 (0.01)	p<0.05
	Colonic brush samples	0.03 (0.07)	0.00 (0.01)	p<0.05
	Faecal samples	0.22 (0.50)	0.00 (0.00)	p=0.14
Peptostreptococcaceae_[XI][G-2]	All samples	0.00 (0.01)	0.00 (0.00)	p=0.05
	Colonic brush samples	0.00 (0.01)	0.00 (0.00)	p=0.05
	Faecal samples	0.00 (0.00)	0.00 (0.00)	p=1.00
Lachnoanaerobaculum	All samples	1.21 (1.43)	1.88 (2.24)	p=0.09
	Colonic brush samples	1.38 (1.55)	2.41 (2.36)	p<0.05
	Faecal samples	0.69 (0.77)	0.29 (0.15)	p=0.09
Lachnospiraceae_[G-7]	All samples	0.02 (0.06)	0.01 (0.02)	p=0.10
	Colonic brush samples	0.03 (0.07)	0.01 (0.02)	p<0.05
	Faecal samples	0.00 (0.01)	0.02 (0.02)	p=0.13
Escherichia	All samples	0.00 (0.01)	0.01 (0.04)	p=0.12
	Colonic brush samples	0.00 (0.02)	0.01 (0.04)	p=0.25
	Faecal samples	0.00 (0.00)	0.01 (0.01)	p<0.01
Gemella	All samples	0.32 (0.51)	0.21 (0.38)	p=0.23
	Colonic brush samples	0.42 (0.55)	0.28 (0.41)	p=0.21
	Faecal samples	0.01 (0.01)	0.00 (0.00)	p<0.05
Peptostreptococcaceae_[XI][G-4]	All samples	0.01 (0.03)	0.02 (0.03)	p=0.51
	Colonic brush samples	0.01 (0.03)	0.01 (0.02)	p=0.51
	Faecal samples	0.01 (0.01)	0.04 (0.04)	p<0.05
Cardiobacterium	All samples	0.00 (0.00)	0.00 (0.00)	p=0.13
	Colonic brush samples	0.00 (0.00)	0.00 (0.00)	p=0.36
	Faecal samples	0.00 (0.00)	0.00 (0.00)	p=0.05

[◊]Unclassified genus

Chapter 10

Learning curve for mastery of colorectal endoscopic submucosal dissection: Perspectives from a large Japanese cohort

This chapter offers a brief summary a paper published in *JGH Open.* The statement of authorship and a copy of the paper 'Learning curve for mastery of colorectal endoscopic submucosal dissection: Perspectives from a large Japanese cohort' follow over the page.

10.1 Summary

When a colorectal lesion is defined as neoplastic, endoscopic resection is most likely the next step. However, a wide range of techniques can be used for this purpose and must be chosen tailored to the lesion itself and the endoscopist expertise. One of the most complex procedures in interventional endoscopy is the ESD technique. Several studies have shown that although good results can be achieved with this technique, the learning process is troublesome. Due to a relatively high complication rate, one could question when an endoscopist could perform such a complex technique safely and effectively. In this study, we analysed the progress of several ESD trainees regarding the safety and efficacy with which they performed colorectal ESDs.

In this retrospective analysis of a prospectively collected database, consecutive patients undergoing colorectal ESD at Nagoya University Hospital in a 10-year period were studied. As all colorectal ESD trainees at Nagoya University Hospital had previous experience with ESD in the upper gastrointestinal tract and/or in animal models, ESD trainees that had kept their attachment to the Department after their 16th colorectal ESD were convened as the expert group.

During the period of the study, 590 colorectal ESDs, performed on 514 patients by 26 endoscopists were analysed. Although expert endoscopists were assigned more difficult lesions than trainees, they still maintained a higher dissection speed compared to trainees (10.3cm2/h versus 6.7cm2/h). However, the effectiveness (i.e. en-bloc and R0 resection rates) and safety (i.e. perforation and bleeding rates) were found to be similar for both groups.

Therefore, although it took longer, the colorectal ESD trainee was able to achieve similar end results when compared to experts. This endorses the safety of teaching such techniques in academic centres when training is appropriately supervised and targeted to endoscopists with previous exposure to ESDs.

10.2 Statement of authorship

Statement of Authorship

Title of Paper	Learning curve for mastery of colorectal endoscopic submucosal dissection: perspectives from a large Japanese cohort
Publication Status	☑ Published ~~☑ Accepted for Publication~~ ~~☐ Submitted for Publication~~ ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	~~Accepted by~~ ~~Submitted to~~ the journal JGH Open Published in Wiley - Online ISSN: 2397-9070

Principal Author

Name of Principal Author (Candidate)	Leonardo Zorron Cheng Tao Pu		
Contribution to the Paper	Conceptualised and designed the study. Involved in data processing and statistical analyses. Interpreted the results and prepared the manuscript.		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	16/12/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Takeshi Yamamura		
Contribution to the Paper	Conceptualised and designed the study. Participated in data collection, processing, interpretation and critical revision of the manuscript for important intellectual content. Revised, read and approved the final version of the manuscript.		
Signature		Date	28/12/2019

Name of Co-Author	Masanao Nakamura		
Contribution to the Paper	Conceptualised and designed the study. Participated in data interpretation and critical revision of the manuscript for important intellectual content. Revised, read and approved the final version of the manuscript.		
Signature		Date	28/12/2019

Name of Co-Author	Masaya Esaki		
Contribution to the Paper	Participated in data collection, processing, interpretation and manuscript edits. Revised, read and approved the final version of the manuscript.		
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Name of Co-Author	Miguel Ricardo Rodriguez		
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Signature	[redacted]	Date	18/12/2019

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Name of Co-Author	Yoshiki Hirooka		
Contribution to the Paper	Participated in data interpretation and critical revision of the manuscript for important intellectual content. Revised, read and approved the final version of the manuscript.		
Signature		Date	Dec. 23. 2011

Name of Co-Author	Mitsuhiro Fujishiro		
Contribution to the Paper	Participated in data interpretation and critical revision of the manuscript for important intellectual content. Revised, read and approved the final version of the manuscript.		
Signature		Date	Dec 19, 2011

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ORIGINAL ARTICLE

Learning curve for mastery of colorectal endoscopic submucosal dissection: Perspectives from a large Japanese cohort

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Key words
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Author contribution: Leonardo Zorron Cheng Tao Pu, Masanao Nakamura, Takeshi Yamamura, and Yoshiki Hirooka conceptualized and designed the study. Takeshi Yamamura, Masanao Nakamura, Yoshiki Hirooka, and Mitsuhiro Fujishiro were responsible for the study supervision. Leonardo Zorron Cheng Tao Pu, Uayporn Kaosombatwattana, Masaya Esaki, and Takeshi Yamamura were involved in the data extraction. Leonardo Zorron Cheng Tao Pu, Uayporn Kaosombatwattana, Masaya Esaki, Suzanne Edwards, and Takeshi Yamamura were involved in the analysis. All authors contributed to interpreting the data and drafting of the manuscript. Alistair D Burt, Rajvinder Singh, Masanao Nakamura, Takeshi Yamamura, Yoshiki Hirooka, and Mitsuhiro Fujishiro critically revised the manuscript. All authors read and approved the final version of this manuscript.

Abstract

Background and Aim: Endoscopic submucosal dissection (ESD) is a challenging procedure. A dissection speed of ≥9 cm^2/h has been acknowledged as a mark for expertise, alongside a complication rate of ≤5% and en bloc resection rate of ≥90%. However, there is lack of objective information on whether the three measures correlate with each other. This study aims to evaluate the dissection speed, safety, and efficacy of colorectal ESDs performed by experts and trainees.

Methods: Consecutive patients undergoing colorectal ESD at a Japanese hospital (2006–2017) were included in a prospectively collected database. Information on patient demographics, proceduralist, and intra-/postprocedure data was retrieved. The primary outcome was the comparison in dissection speed. The secondary outcomes included differences in safety and efficacy. Log-linear regression models adjusted for confounders (e.g. R0 resection) were used to assess the differences in dissection speed.

Results: Five hundred ninety procedures (514 patients) performed by 26 endoscopists were analyzed. Experts performed a higher number of difficult lesions (e.g. F2 fibrosis) but achieved higher dissection speed (10.3 *vs* 6.7 cm^2/h). The difference was statistically significant for both unadjusted and adjusted models ($P < 0.0001$). The en bloc resection rates were similar for both groups (experts = 95.6%; trainees = 94.7%, $P = 0.61$). Although nonexperts damaged more of the muscularis propria (18.6 *vs* 12.5%, $P = 0.04$), this did not translate into a significant difference in perforation (experts = 3.7%; trainees = 6.9%, $P = 0.09$) or delayed bleeding (experts = 2.9%; trainees = 4.4%, $P = 0.34$). The dissection speed steadily increased with expertise.

Conclusion: Although dissection speed for colorectal ESD was significantly higher for experts, ESDs could be safely and efficaciously performed by ESD trainees.

Introduction

Endoscopic resection is the current gold standard for treatment of precancerous and early cancerous lesions within the gastrointestinal tract. Different modalities of endoscopic resection have been proposed and the decision of one over the other depends on several factors, one being the degree of dysplasia/

invasiveness of the lesion. For lesions involving superficial submucosa, guidelines from both West and East advise on the use of endoscopic submucosal dissection (ESD).[1–4]

There are different learning curves depending on endoscopist factors such as prior experience with other therapeutic endoscopy procedures (e.g. endoscopic mucosal resection [EMR]) and experience in assisting ESDs.[5] Different learning curves depend on the endoscopist's expertise and the location of the ESD within the gastrointestinal tract. As ESDs performed in the stomach are easier to tackle than in the esophagus and rectum/colon, it is advised to use gastric ESDs first for ESD training.[6] This is feasible in Asian countries owing to their relatively high prevalence of early gastric cancer. However, in Western countries, this is not a reality, and hence the choice for training falls into the lower gastrointestinal tract.

In selected scenarios, a few dozens of ESDs performed in humans suffice for achieving proficiency. Fewer cases are thought to be necessary if animal models are used for training before performing in humans.[7] However, this has been mainly postulated based on gastric ESDs. Although there are studies looking into colorectal ESD learning curves in both the West and East, they mainly focus on single-operator experiences.[8–10]

A definitive number of procedures to achieve proficiency in ESD is difficult to determine. This is not only due to variation in personal skills, but also due to the lack of objective standardized markers for expertise. In order to determine the minimum standards for ESD skills, a group of experts gathered evidence from multiple studies and advised thresholds for "ESD proficiency," mainly based on three variables. According to Oyama *et al.*, for an endoscopist to be considered skilled in ESD, he or she should achieve: (i) dissection speed ≥9 cm^2/h; (ii) complication rate ≤5%; and (iii) en bloc resection rate ≥90%.[11] However, objective information on how these three measures behave throughout the ESD learning curve is scarce. In this study, we intend to evaluate the learning curve of a Japanese endoscopist cohort in gaining proficiency toward colorectal ESD. As proposed by Oyama *et al.*, we specifically investigated the evolution of dissection speed, safety, and efficacy throughout the process.

Methods

We retrospectively assessed the Nagoya University Hospital's prospective database of colorectal ESDs and included all the patients who were submitted to colorectal ESDs from 2006 to 2017. The final decision of proceeding with the ESD was made based on endoscopic imaging after topical administration of 0.4% indigo carmine, virtual chromoendoscopy (either narrow-band imaging [NBI] or blue-laser imaging [BLI]), and crystal violet at 0.05%. From this initial cohort, only the endoscopists who had performed more than one ESD during his or her attachment to the department were included in the study.

We divided colorectal ESDs into two groups according to the executor: ESD trainee group and ESD expert group. Each ESD trainee performed on average 16 colorectal ESDs in our center before finishing the colorectal ESD supervised training program. Subjectively, the trainees who completed their training were considered proficient in our center. Therefore, the ESD expert group consisted of those in the ESD trainee group who continued with their attachment to the department after their 16th colorectal ESD. In other words, if an endoscopist had performed 20 colorectal ESDs while at Nagoya University Hospital, the data on the first 16 ESDs were used for the ESD trainee group and the last 4 were used for the ESD expert group. All endoscopists included in the ESD expert group had their initial 16 colorectal ESDs included in the ESD trainee group.

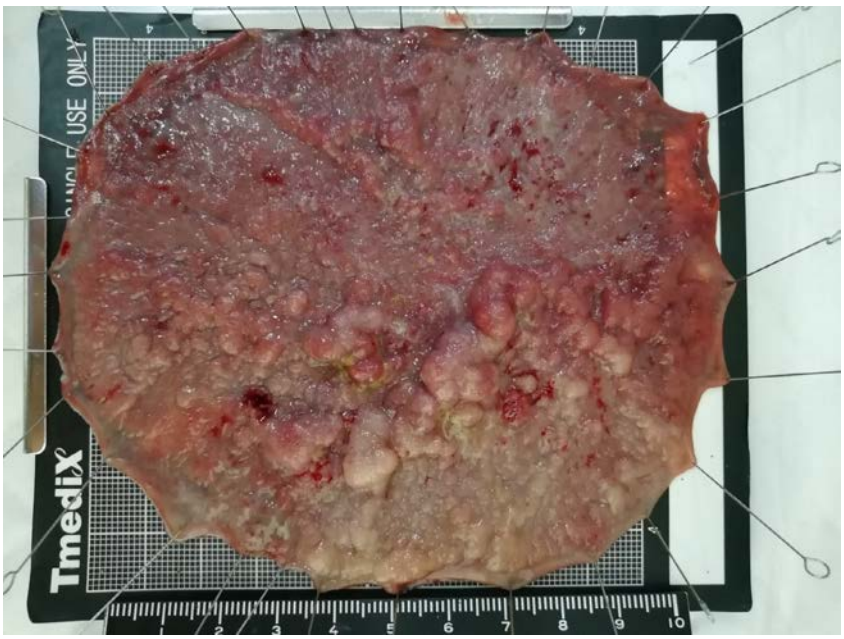

Figure 1 Example of endoscopic submucosal dissection specimen measurement.

We retrieved information on patient demographics, lesion endoscopy and pathology features, and procedure details (e.g. time for completion). The size of each lesion was measured with a ruler after resection and fixation onto a plate (Fig. 1—Example of ESD specimen measurement). Lesion areas were calculated according to their shape (circular or oval) and based on the two major measured diameters after resection ($\pi \times$ length $\times$ width/4), and expressed in cm^2. The area was then divided by the procedure time in hours for determining the average dissection speed in cm^2/h. Procedure time was defined as the time from first incision until the retrieval of the specimen (including the time for management of complications). Fibrosis was expressed in three categories (i.e. F0-2) as previously described.[12] Complications included intraprocedure muscularis propria (MP) damage (excluding perforation), perforation, post-colorectal ESD coagulation syndrome (PECS), delayed bleeding (that required endoscopy or surgery after ESD), abdominal pain (promptly after the procedure), and fever (temperature above 37.5°C). Curative resection was defined as ESD R0 procedures for patients with lesions up to 1000 μm into the submucosa. PECS was defined as abdominal pain without perforation as per Arimoto *et al.*[13]

The primary outcome was to analyze the differences in average dissection speed between colorectal ESD trainees and experts. The secondary outcomes included the differences in safety and efficacy between the two groups.

Procedures were performed after split bowel preparation, using conscious sedation and carbon dioxide insufflation. The injectate fluid was prepared with hyaluronic acid and saline in a 1:1 proportion and had adrenaline in a 1:200 000 dilution. A small amount of indigo carmine (~1 mL/200 mL) was also added to the solution. The main knife used for dissection was Flush Knife BT-S 2.0 (©Fujifilm Corporation, Tokyo, Japan) and that used for bleeding control was Coagrasper (©Olympus, Tokyo, Japan). This was connected to a water jet pump (Fujifilm JW-2 or Olympus OFP-2) with saline dyed lightly blue by indigo carmine. The video endoscopes used were either from Fujifilm (600 series) or Olympus (260 series) and as a rule consisted of pediatric colonoscopes for lesions in the right colon and gastroscopes for lesions in the left colon. All ESDs involved the use of disposable distal hoods (©TOP Corporation M-02, Tokyo, Japan). For electrical cutting and coagulation, VIO ICC 200, 300 D, or 3GI was used as the power source (ERBE Elektromedizin, Tübingen, Germany). The standard settings for ESD in our center are Endocut I effect 2; forced coagulation effect 2, 40 W; and soft coagulation effect 5, 60 W. For adverse event monitoring, all patients stayed in the hospital for 1 week after the colorectal ESD. Specialist gastrointestinal pathologists assessed the ESD specimen in all cases.

Log-linear regression models adjusted for a priori confounders were used for determining differences in dissection speed. Confounders included difficulty (fibrosis score, lifting sign, ileocecal [IC] valve or anus involvement, lesion beyond fold, retrograde position use, and lesion size), safety (MP damage, any complication, delayed bleeding, perforation, PECS, and emergency operation), and efficacy variables (R0 resection, curative resection, and en bloc resection). Chi-squared tests were used to assess the differences between proportions, and Student's *t*-tests were used to assess differences between means using the MedCalc calculator (©2019 MedCalc Software bvba, Ostend, Belgium). The statistical software used to perform adjusted log-linear models was SAS 9.4 (SAS Institute Inc., Cary, NC, USA). *P* values < 0.05 were considered significant. This study was approved by the Nagoya University Hospital Human Ethics Review Committee under the number

Table 1 Cohort characteristics per group

n (%)	Experts	ESD trainees	*P*-value
Number of ESDs, *n* (%)	272 (100)	318 (100)	NA
Male, *n* (%)	169 (62.1)	188 (59.1)	0.46
Age in years, average (SD)	67.8 (10.8)	67.8 (11.5)	0.97
Right colon location, *n* (%)	97 (35.7)	113 (35.5)	0.96
Rectum location, *n* (%)	87 (32.0)	114 (35.8)	0.33
Adenomas, *n* (%)	58 (21.3)	56 (17.6)	0.26
M adenocarcinomas, *n* (%)	149 (54.8)	176 (55.3)	0.90
Superficial adenocarcinomas†, *n* (%)	29 (14.9)	25 (11.5)	0.22
Invasive adenocarcinomas†, *n* (%)	16 (8.2)	17 (7.8)	0.86
Carcinoid, *n* (%)*	3 (1.1)	12 (3.8)	0.04
Other, *n* (%)	17 (6.3)	32 (10.1)	0.10

*$P < 0.05$.

†Threshold of 1000 micrometers into the submucosa.

N/A, not applicable; ESD, endoscopic submucosal dissection.

Table 2 Endoscopic submucosal dissection (ESD) outcomes per group model 2

	Experts	ESD trainees	*P*-value
Procedure speed in cm^2/h, mean (SD)*	10.3 (13.1)	6.7 (7.6)	<0.001
Procedure time in minutes, mean (SD)*	98.8 (73.0)	119.9 (71.1)	<0.001
Specimen area in cm^2, mean (SD)*	15.1 (16.8)	12.6 (10.7)	0.03
En-bloc resection, *n* (%)	260 (95.6)	301 (94.7)	0.61
R0 resection, *n* (%)	233 (85.7)	266 (83.7)	0.50
Curative resection, *n* (%)	221 (81.3)	258 (81.1)	0.95
Beyond fold, *n* (%)*	171 (62.9)	165 (51.9)	<0.01
F2 fibrosis, *n* (%)*	54 (19.9)	39 (12.3)	0.01
Ileocecal valve or anus involvement, *n* (%)*	27 (9.9)	14 (4.4)	<0.01
Muscularis propria damaged, *n* (%)*	34 (12.5)	59 (18.6)	0.04
Fever (>37.5°C), *n* (%)	32 (11.8)	39 (12.3)	0.85
PECS, *n* (%)	19 (7.0)	23 (7.2)	0.93
Perforation, *n* (%)	10 (3.7)	22 (6.9)	0.09
Delayed bleeding, *n* (%)	8 (2.9)	14 (4.4)	0.34
Emergency operation, *n* (%)	0 (0.0)	2 (0.6)	0.19

*$P < 0.05$.

Adjusted log linear regression of procedure speed (in cm/h) *versus* expertise and relevant confounders.

PECS, post-colorectal ESD coagulation syndrome.

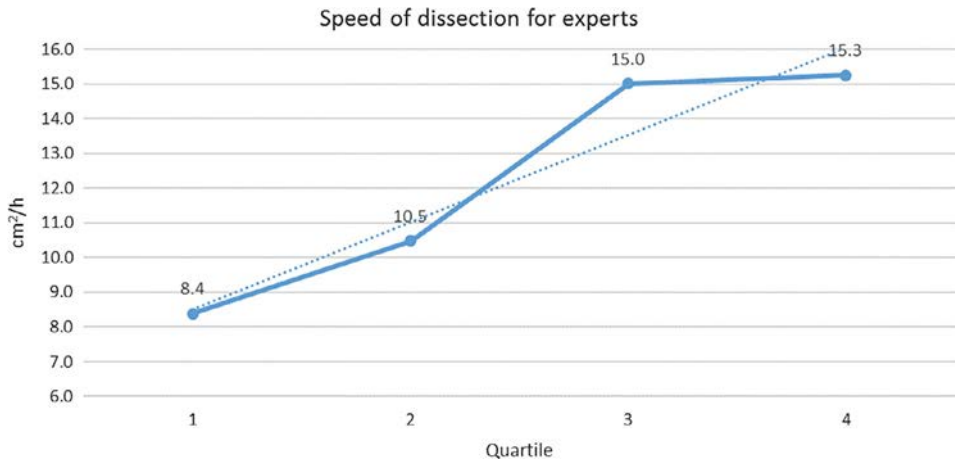

Figure 2 Endoscopic submucosal dissection speed evolution for expert endoscopists.

2015-0485. All data were coded, and patient anonymity was guaranteed for all nonessential/nonmedical personnel.

This study has been approved by the Ethics Review Committee from Nagoya University Hospital.

Results

Six hundred fifteen ESD procedures performed in 529 patients between 2006 and 2017 were initially assessed. Thirty-six endoscopists participated in these procedures. Twenty-five ESDs from 15 patients performed by 10 endoscopists were excluded from the analysis (endoscopist with only one ESD or procedure aborted after advanced imaging). The final dataset of 590 procedures from 514 patients performed by 26 endoscopists were analyzed. Two hundred seventy-two (46.1%) procedures were performed by the expert group. The mean patient age was 67.8 (SD = 11.2) and 357 (60.5%) were male. The average major diameter of the specimen was 3.5 cm (SD = 1.8) and the average area was 13.7 cm^2 (SD = 13.9). An average of 110 min (SD = 72.7) was required to complete the ESD. The descriptive statistics for ESD trainees and experts are summarized in Table 1.

Of the 26 ESD trainees, 13 had performed more than 16 ESDs in our center and hence continued as part of the expert group. Two hundred seventy-two (46.1%) of the procedures were performed by the expert group. The most common histology was mucosal adenocarcinoma (55.1%). Despite experts having a significantly higher number of difficult lesions (i.e. larger, fibrotic, and/or difficult position), they achieved higher dissection speed (10.3 vs. 6.7 cm^2/h). This difference was statistically significant for both unadjusted and adjusted models (both having $P < 0.0001$). The en bloc (experts = 95.6%; trainees = 94.7%, $P = 0.61$) and R0 (experts = 85.7%; trainees = 83.6%, $P = 0.50$) resection rates were similar for both groups. Although nonexperts damaged more of the muscularis propria (18.6 *vs* 12.5%, $P = 0.04$), this did not translate into a significant difference in perforation (experts = 3.7%; trainees = 6.9%, $P = 0.09$) or

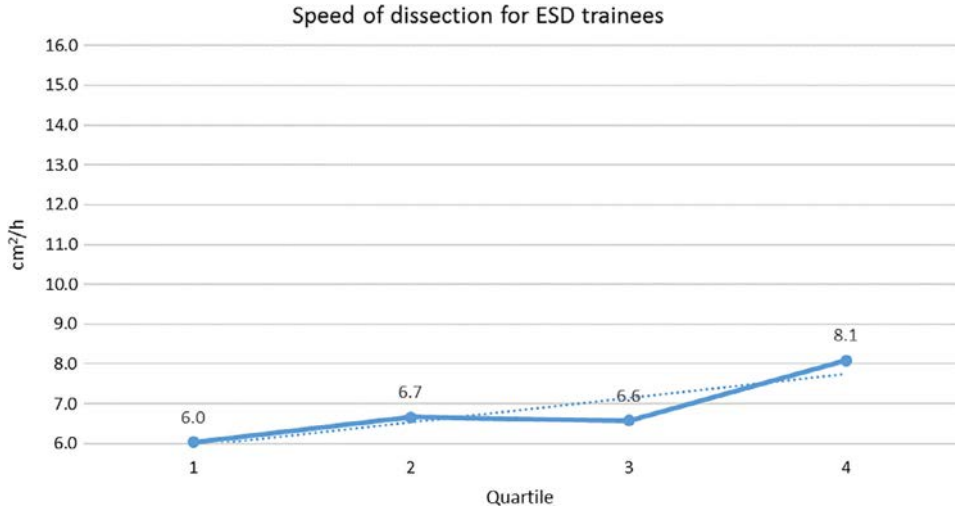

Figure 3 Endoscopic submucosal dissection (ESD) speed evolution for ESD trainees.

delayed bleeding (experts = 2.9%; trainees = 4.4%, $P = 0.34$). Curative resection was not different between the groups (experts = 81.3%; trainees = 81.1%, $P = 0.95$). Efficacy and safety variables have been summarized in Table 2.

The dissection speed steadily increased with expertise. The trend of improvement in dissection speed is illustrated in Figure 2 (ESD dissection speed evolution for expert endoscopists) and Figure 3 (ESD dissection speed evolution for ESD trainees). In the adjusted log-linear regression, eight variables were found to present statistically different results regarding average dissection speed: experience, fibrosis, curative resection, en bloc resection, free margins, lesion size, involvement of folds, and damage to muscularis propria, which independently affected speed ($P < 0.05$). ESDs performed by the expert group, with F0 fibrosis, with curative and en bloc resections, with free margins and without MP damage led to a higher average dissection speed. Interestingly, larger size and lesion over the fold were also associated with higher speed.

The data on average speed of dissection were divided into quartiles for better understanding of the evolution of each group. The quartiles were based on the total number of procedures performed by each group (ESD trainees and experts) divided by 4. For instance, all ESD trainees were allocated into Quartile 1 up to their fourth ESD, when they then passed through to Quartile 2. ESD experts were allocated into Quartile 1 up to their 25th ESD, when they then passed through to Quartile 2.

Discussion

In our study, we have arbitrarily adopted 16 as the number of colorectal ESDs performed to be allocated into the "expert group." This was considered sufficient based on previous ESD experience of the trainees (20–50 ESDs) and on the average number of colorectal ESDs performed by the trainees during their colorectal ESD training. Although the number of procedures to achieve proficiency is variable in the literature, our data suggest that a few dozen allow a safe and effective ESD. Moreover, this could be achieved even though it is performed at a slower pace. Hotta *et al*. studied 120 lesions and found a minimum number of 40 ESDs to avoid perforation and 80 to reach R0 rates similar to experts. This study was based on the data from a single expert endoscopist in Japan.[14] A single Western operator with a similar background (i.e. hundreds of EMRs and few gastric ESDs) have shown a higher number of ESDs required for reaching the improvement plateau. After 152 procedures, the en bloc (R0) resection rate achieved was 92.4%. The speed of dissection has reached the 9 cm^2/h threshold with 76 cases.[15] Another single-operator large cohort has found that although it was possible to reach expert-level dissection speed and en bloc resection rates after over 300 colorectal ESDs, it was not possible to achieve the R0 nor complication rates expected for an expert.[16] On the other hand, another single-operator study from Germany has found numbers close to the expert standards with only 30 unsupervised cases.[17] These studies illustrate the immense variability found, which is likely to be associated with endoscopist-related factors. Hence a comprehensive study on learning curves for multiple endoscopists is important to accurately evaluate ESD training and achievement of expertise, mitigating the bias of individual particularities.

Some factors might influence the dissection speed such as fibrosis, difficult locations, and lesion size. They were taken into account in a log-linear adjusted model and it was confirmed that even controlling for these factors, experts achieved higher dissection speed compared with ESD trainees. As endoscopists' expertise in ESD increases, so does the complexity of cases (e.g. larger lesions and more difficult locations) and the dissection speed. These may bias the outcomes toward a worse complication rate for experts.[18] However, we have found that although the complexity and dissection speed were indeed higher for experts, the complications were not. Looking at the dissection speed graph evolution throughout the first and second half of procedures for ESD trainees and experts, it is possible to visualize a trend of continuity in learning and evolution through time.

Being one of the most complex procedures in gastrointestinal endoscopy, ESD comes with relative high risk of complications such as bleeding and perforation. Although the perforation and bleeding rates were numerically higher in the ESD trainee group, they were not statistically different from the expert group. Therefore, ESDs were safely performed and with similar efficacy (i.e. R0 and en bloc resection rates) by both ESD trainees and experts. This might sound unusual if only the number during the colorectal ESD training is considered. However, ESD during training is always supervised by an expert and all of our colorectal ESD trainees had previous experience with ESD. A recent meta-analysis with 97 studies on ESDs found an overall perforation rate of 5.2% and a delayed bleeding rate of 2.7%. These rates varied depending on where the study took place. On the one hand, the pool of Asian studies had perforation and bleeding rates of 4.5 and 2.4%. On the other hand, the sum of non-Asian studies had perforation and bleeding rates of 8.6 and 4.2%.[19] Our study has shown a rate of perforation and delayed bleeding closer to other Asian studies.

In this study, the average dissection speed steadily increased over time for both ESD trainee group and expert group. Interestingly, even with a slower dissection speed than recommended (or because a slower and more cautious dissection was utilized), serious complications were not statistically different compared to experts. The fact that all ESDs performed by ESD trainees were supervised certainly contributed to this outcome. Nevertheless, knowing that ESD trainees can perform as safely and as efficaciously compared experts (when supervised) might be an important information for training centers. In addition, conversely to good outcomes regarding curative resection and complications, the dissection speed was always lower than the recommended 9 cm^2/h for ESD trainees. This suggests adequate safety and efficacy outcomes might not be intertwined with dissection speed of 9 cm^2/h or higher.

The limitations of this study include the low threshold for being considered an expert (only 16 colorectal ESDs) and the fact that all ESDs performed by the trainees were always supervised by an expert. Although only 16 colorectal ESDs were considered as a threshold for this study for logistic purposes, the results suggest that this number might be sufficient. Endoscopists selected for the colorectal ESD training program at Nagoya University Hospital must have prior experience with ESD in animal models and/or humans (between 20 and 50 ESDs).

In our center, all colorectal ESDs performed by the trainees are supervised by experts. It is expected that when

supervised, the complication rates should be lower than when ESDs are performed without supervision. Therefore, our results might reflect only the early learning phase performance when this is done under supervision. However, as it is advised that initially ESDs should always be performed under supervision, our results are likely to be applicable to most cases of early learning curve for colorectal ESD. In addition, all our ESD experts have originated from following-up ESD trainees. Therefore, it is possible to say that even after finishing the training and not being under supervision, "early ESD experts" were capable of maintaining/improving their dissection speed, efficacy, and safety when performing colorectal ESDs.

In conclusion, although dissection speed for colorectal ESD was significantly higher for experts, ESDs could be safely and efficaciously performed by ESD trainees.

References

1 Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T *et al*. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*. 2015; **47**: 829–54.
2 Maple JT, Abu Dayyeh BK, Chauhan SS *et al*. Endoscopic submucosal dissection. *Gastrointest. Endosc.* 2015; **81**: 1311–25.
3 Tanaka S, Kashida H, Saito Y *et al*. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig. Endosc.* 2015; **27**: 417–34.
4 Fujishiro M, Yahagi N, Kakushima N *et al*. Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases. *Clin. Gastroenterol. Hepatol.* 2007; **5**: 678–83.
5 Tsuji Y, Ohata K, Sekiguchi M *et al*. An effective training system for endoscopic submucosal dissection of gastric neoplasm. *Endoscopy*. 2011; **43**: 1033–8.
6 Niimi K, Fujishiro M, Goto O, Kodashima S, Koike K. Safety and efficacy of colorectal endoscopic submucosal dissection by the trainee endoscopists. *Dig. Endosc.* 2012; **24** (Suppl. 1): 154–8.
7 Ohata K, Nonaka K, Misumi Y *et al*. Usefulness of training using animal models for colorectal endoscopic submucosal dissection: is experience performing gastric ESD really needed? *Endosc. Int. Open*. 2016; **4**: E333–9.
8 Iacopini F, Bella A, Costamagna G *et al*. Stepwise training in rectal and colonic endoscopic submucosal dissection with differentiated learning curves. *Gastrointest. Endosc.* 2012; **76**: 1188–96.
9 Toyonaga T, Man-i M, East JE *et al*. 1,635 Endoscopic submucosal dissection cases in the esophagus, stomach, and colorectum: complication rates and long-term outcomes. *Surg. Endosc.* 2013; **27**: 1000–8.
10 Saito Y, Uraoka T, Yamaguchi Y *et al*. A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). *Gastrointest. Endosc.* 2010; **72**: 1217–25.
11 Oyama T, Yahagi N, Ponchon T, Kiesslich T, Berr F. How to establish endoscopic submucosal dissection in Western countries. *World J. Gastroenterol.* 2015; **21**: 11209–20.
12 Matsumoto A, Tanaka S, Oba S *et al*. Outcome of endoscopic submucosal dissection for colorectal tumors accompanied by fibrosis. *Scand. J. Gastroenterol.* 2010; **45**: 1329–37.
13 Arimoto J, Higurashi T, Kato S *et al*. Risk factors for post-colorectal endoscopic submucosal dissection (ESD) coagulation syndrome: a multicenter, prospective, observational study. *Endosc. Int. Open*. 2018; **6**: E342–e9.
14 Hotta K, Oyama T, Shinohara T *et al*. Learning curve for endoscopic submucosal dissection of large colorectal tumors. *Dig. Endosc.* 2010; **22**: 302–6.
15 Spychalski M, Skulimowski A, Dziki A, Saito Y. Colorectal endoscopic submucosal dissection (ESD) in the West – when can satisfactory results be obtained? A single-operator learning curve analysis. *Scand. J. Gastroenterol.* 2017; **52**: 1442–52.
16 Rönnow CF, Uedo N, Toth E, Thorlacius H. Endoscopic submucosal dissection of 301 large colorectal neoplasias: outcome and learning curve from a specialized center in Europe. *Endosc. Int. Open*. 2018; **6**: E1340–e8.
17 Ebigbo A, Probst A, Römmele C, Messmann H. Step-up training for colorectal and gastric ESD and the challenge of ESD training in the proximal colon: results from a German Center. *Endosc. Int. Open*. 2018; **6**: E524–e30.
18 Kakushima N, Fujishiro M, Kodashima S, Muraki Y, Tateishi A, Omata M. A learning curve for endoscopic submucosal dissection of gastric epithelial neoplasms. *Endoscopy*. 2006; **38**: 991–5.
19 Fuccio L, Hassan C, Ponchon T *et al*. Clinical outcomes after endoscopic submucosal dissection for colorectal neoplasia: a systematic review and meta-analysis. *Gastrointest. Endosc.* 2017; **86**: 74–86.e17.

Chapter 11

Narrow band imaging for scar (NBI-SCAR) classification: from conception to multicenter validation

This chapter offers a brief summary, as well as a copy (.pdf) of a paper published in *Gastrointestinal Endoscopy*. The statement of authorship and paper (.pdf) 'Narrow band imaging for scar (NBI-SCAR) classification: From conception to multicentre validation' follow over the page.

11.1 Summary

It is common for large and/or piecemeal endoscopic resections to leave a scar, and these are advised to be followed-up within six months. According to current standards, endoscopic imaging is not considered to be sufficiently accurate to substitute scar biopsies during surveillance, even when there are no signs of recurrence. However, only 10-20% of large polyps removed in a piecemeal fashion have a recurrence of neoplastic tissue within the scar. That is, 80-90% of the scars post piecemeal resection that are biopsied come back with results negative for neoplastic tissue.

In recent years, researchers have investigated how the advances in endoscopic imaging, specifically the use of NBI, could allow for the acceptance of endoscopic imaging as a substitute for biopsy. Although good results have been achieved for ruling out recurrence, the lack of a standardised endoscopic classification has made this approach unlikely to be widely accepted. In this study, we developed and tested an endoscopic classification based on NBI for predicting recurrence in post endoscopic resection scars.

Initially, endoscopic features for predicting recurrence were defined based on colour, capillary and pit patterns. Scars with at least two concordant characteristics were diagnosed with 'high confidence' for the NBI-SCAR classification. Patients with scars were then prospectively enrolled and assessed in real-time with high-definition white light endoscopy (HDWLE) followed by uNBI-DF in the exploratory phase. This was followed by a validation phase, which consisted of enrolling endoscopists from six different endoscopy settings (Australia, United States, Japan, Brazil, Singapore and Malaysia) to evaluate 10 one-minute videos of post-ER scars on uNBI-DF.

The validation took place over two sessions separated by two to three weeks. 100 scars from 82 patients were assessed in the exploratory phase and showed a higher sensitivity to the NBI-SCAR classification compared to HDWLE prediction (100% versus 73.7%). Similar results were achieved in the validation phase for endoscopists who routinely perform colonoscopies and use NBI (sensitivity of 96.4%). The inter- and intra-rater reliability of the NBI-SCAR classification throughout all centres were respectively substantial (k=0.61) and moderate (average S=0.52).

This research corroborates the findings of previous studies and introduces a classification that could potentially be used as a standard for ruling out recurrence, substituting biopsies when prediction is made with high confidence.

11.2 Statement of authorship

Statement of Authorship

Title of Paper	Narrow Band Imaging for scar (NBI-SCAR) classification: from conception to multicenter validation
Publication Status	☑ Published ~~☑ Accepted for Publication~~ ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	~~Accepted for publication~~ Published in the Gastrointestinal Endoscopy journal (Online ISSN: 1097-6779 Print ISSN: 0016-5107)

Principal Author

Name of Principal Author (Candidate)	Leonardo Zorron Cheng Tao Pu		
Contribution to the Paper	Conceptualised and designed the study. Participated in data extraction, statistics and interpretation of results. Drafted the manuscript.		
Overall percentage (%)	60		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	30/08/2019

Co-Author Contributions

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i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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ORIGINAL ARTICLE

Narrow-band imaging for scar (NBI-SCAR) classification: from conception to multicenter validation

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Background and Aims: Surveillance post–endoscopic resection (ER) currently warrants biopsy samples from the resection site scar in most cases, although clinical practice is variable. A classification with standard criteria for scars has not yet been established. We aimed to create and validate a novel classification for post-ER scars by using specific criteria based on advanced imaging.

Methods: Key endoscopic features for scars with and without recurrence were (1) dark brown color, elongated/branched pit pattern, and dense capillary pattern and (2) whitish, pale appearance, round/slightly large pits, and irregular sparse vessels. Scars were first assessed with high-definition white-light endoscopy (HD-WLE) followed by interrogation with narrow-band imaging (NBI). Scars with at least 2 concordant characteristics were diagnosed with "high confidence" for NBI for scar (NBI-SCAR) classification. The final endoscopic predictions were correlated with histopathology. The primary outcome was the difference in sensitivity between NBI-SCAR and HD-WLE predictions. Secondary outcomes included the validation of our findings in 6 different endoscopy settings (Australia, United States, Japan, Brazil, Singapore, and Malaysia). The validation took place in 2 sessions separated by 2 to 3 weeks, each with 10 one-minute videos of post-ER scars on underwater NBI with dual focus. Inter-rater and intrarater reliability were calculated with Fleiss' free-marginal kappa and Bennett et al. S score, respectively.

Results: One hundred scars from 82 patients were included. Ninety-five scars were accurately predicted with high confidence by NBI-SCAR in the exploratory phase. NBI-SCAR sensitivity was significantly higher compared with HD-WLE (100% vs 73.7%, $P < .05$). In the validation phase, similar results were found for endoscopists who routinely perform colonoscopies and use NBI (sensitivity of 96.4%). The inter-rater and intrarater reliability throughout all centers were, respectively, substantial ($\kappa = .61$) and moderate (average $S = .52$) for this subset.

Conclusions: NBI-SCAR has a high sensitivity and negative predictive value for excluding recurrence for endoscopists experienced in colonoscopy and NBI. In this setting, this approach may help to accurately evaluate or resect scars and potentially mitigate the burden of unnecessary biopsy samples. (Gastrointest Endosc 2019;■:1-9.)

(footnotes appear on last page of article)

Endoscopic resection (ER) of neoplastic polyps is an important step in colorectal cancer prevention. The timing of follow-up colonoscopy is mainly based on the histologic nature and size of lesions, but some types of resection (eg, piecemeal EMR) are advised to have a closer follow-up for assessment of recurrence.[1] Follow-up colonoscopy after large piecemeal EMR is usually performed after a 4- to 6-month interval. Larger lesion size, presence of bleeding during the procedure, and high-grade dysplasia have been found to be independent risk factors for recurrence in a multivariate analysis of more than 1000 lesions.[2]

Surveillance colonoscopy post-ER commonly identifies scar tissue at the site of resection, especially after ER of large lesions. Most guidelines recommend that targeted biopsy sampling of the resection site should be performed to exclude histopathologic evidence of recurrence.[3-5]

However, the yield of this approach is low because recurrence is relatively uncommon after ER.[6,7] Further, sampling error can occur, leading to false-negative results.

Over the years, with development of better endoscopic systems equipped with high-definition (HD) video imaging and magnification narrow-band imaging (NBI), we are now able to examine and describe the mucosal surface in finer detail. The application of advanced endoscopic imaging may increase our capability to rule out recurrence at the post-ER scar site. Several aspects of the scar are used as endoscopic predictors, some of which have been investigated in a recent study by Desomer et al.[8] Despite describing in detail the steps to evaluate the scar, Desomer et al reverted to the Kudo pit pattern to identify neoplastic pattern. This step, which requires indigo carmine/methylene blue chromoendoscopy, makes the proposal of a simple and direct classification using solely NBI more appealing. NBI also has an advantage over other advanced endoscopic imaging modalities (eg, confocal endomicroscopy), because NBI is much more widely available and easy to use by practicing endoscopists, even outside of expert centers.[9]

In summary, although Desomer et al[8] demonstrated high accuracy and sensitivity by adopting a systematic approach to look at scars, no formal classification was proposed. This leaves the systematic approach dependent on use of the Kudo classification, which may be more difficult to implement. We propose that the development of a well-defined and simple methodology to evaluate post-ER scars may be an important approach to more accurately identify recurrence.[5] Therefore, this study was designed to evaluate the use of a simple standardized classification for prediction of recurrence in post-ER scars, which we named NBI for scar (NBI-SCAR) classification.

METHODS

Because our main objective was to rule out recurrence, a sample size was chosen based on the conservative estimate of 15% sensitivity difference between HD white-light endoscopy (HD-WLE) and NBI-SCAR groups, based on Desomer et al.[8] For a 95% confidence interval and 80% power, the required number was 97 scars.

Inclusion criteria consisted of patients over 18 years of age referred for colonoscopy at the Endoscopy Unit of Lyell McEwin Hospital who presented a post-ER scar. The colonoscopes used were HQ190 series (Olympus, Tokyo, Japan). Pregnant women, emergency colonoscopies, and patients unwilling to participate were excluded. Standard split-dose bowel preparation with sodium picosulfate and polyethylene glycol was used for all patients. All procedures were performed using carbon dioxide with the patient under sedation by an anesthesiologist or nurse sedationist.

This study was approved by the Human Research Ethics Committee (TQEH/LMH/MH) under the reference number 2008128. This Committee is constituted in accordance with the NHMRC National Statement on Ethical Conduct in Human Research (2007) and incorporating all updates.

All patients had their scars evaluated with a cap and underwater (clear water) technique in regard to 3 features: color, pit pattern, and vascularity. These features were determined by consensus among the authors. The 3 features chosen for the classification were selected mainly based on the well-established colorectal polyp classifications such as the NBI International Colorectal Endoscopic classification.[10,11] The exact description of each feature was further refined with an image library of 50 prospectively collected underwater scar images. The conceptualization and determining features for the NBI-SCAR were carried out before the enrollment of the first patient for this study. The 2 endoscopists who participated in the conceptualization of the NBI-SCAR classification also participated in the exploratory phase and have over 10 years (R.S.) and over 3 years (L.Z.C.T.P.) of experience with advanced endoscopic imaging.

Key features of scars with recurrence have been established as follows: dark brown color, elongated or branched pit pattern, and dense capillary pattern surrounding pits. Scars with no recurrence have been established reverse features: a whitish, pale appearance; round and slightly larger pits compared with the surroundings; and irregular sparse vessels with no change in caliber. The NBI-SCAR classification is summarized in Figure 1. If 2 or more concordant key features were found, a high-confidence diagnosis was made. If 1 key feature was found but 2 others were not able to be defined (eg, whitish/pale color, no visible pits, and no discernible vascularity), the scar was predicted with low confidence toward the key feature identified. If none of the 3 key features was identified or if 2 contrasting key features were identified alongside 1 no-identifiable key feature, the diagnosis with the NBI-SCAR classification was deemed as not possible.

The primary outcome was the difference in sensitivity of HD-WLE and NBI-SCAR for detecting recurrence on scars. Secondary outcomes included accuracy measures for overall and high confidence diagnoses with HD-WLE and NBI-SCAR and accuracy and inter/intraobserver agreement of the NBI-SCAR classification in different endoscopy centers around the world (ie, Japan, United States, Brazil, Singapore, Malaysia, and Australia).

In the exploratory phase, the scar was initially evaluated with HD-WLE followed by underwater NBI with dual focus (uNBI-DF) in real time by 2 endoscopists (R.S. and L.Z.C.T.P.). If the 2 endoscopists disagreed regarding 1 feature, that feature was deemed as "not possible to be diagnosed." Scars with at least 2 concordant characteristics were diagnosed with high confidence for NBI-SCAR. HD-WLE diagnosis was considered of high confidence if agreed upon by 2 endoscopists. The final endoscopic prediction was correlated with the biopsy sample of the scar.

The validation phase was conceived in the form of a 2-session test, where both trainees (ie, advanced

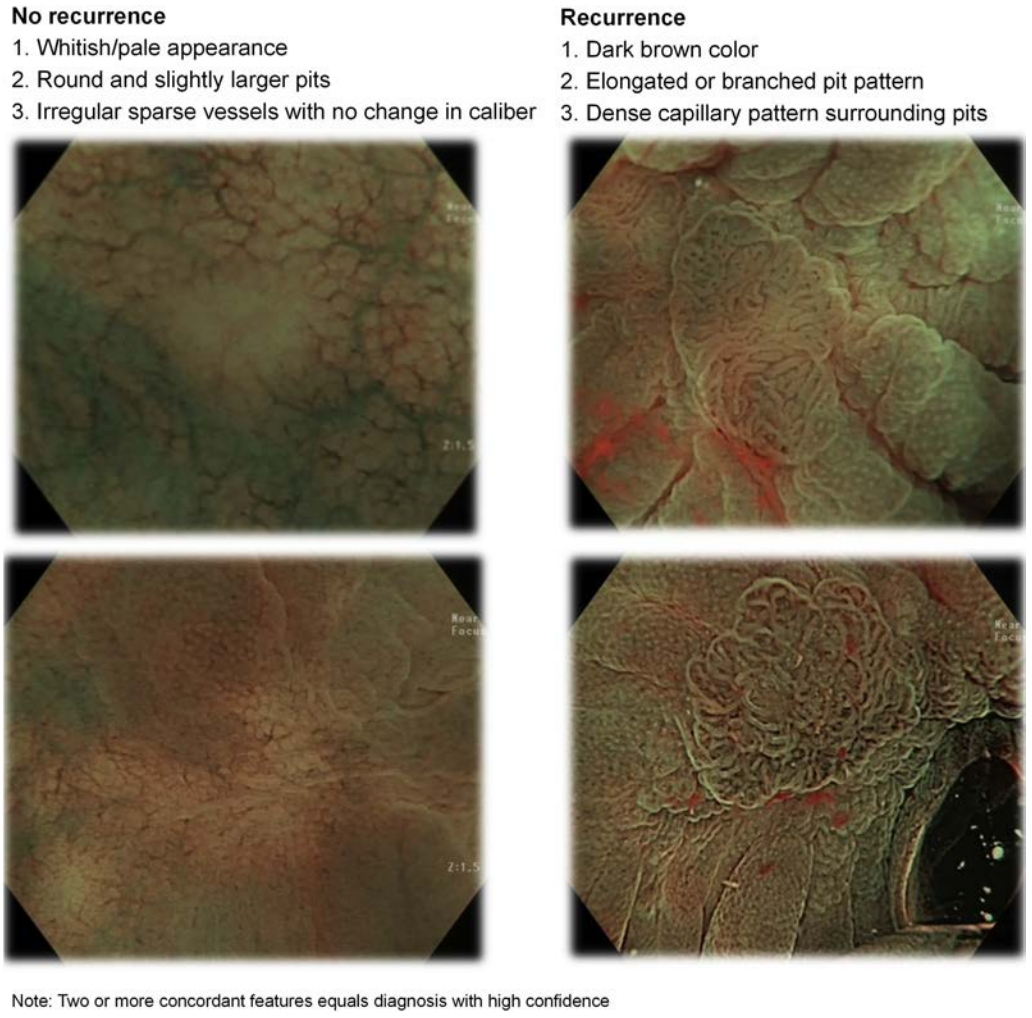

Figure 1. Narrow-band imaging for scar classification.

endoscopy trainees or fellows) and experienced endoscopists (ie, consultants, after formal training) without prior exposure to the NBI-SCAR classification were invited to participate. This was carried out in 6 countries: Japan, United States, Brazil, Singapore, Malaysia, and Australia. None of the invited endoscopist raters was previously familiar with the proposed classification scheme. A formal explanation about the NBI-SCAR was provided in the form of a printed version of the classification, which was given to participants 1 day before the first session took place for familiarization. The recommended time for studying the classification before the test was 10 minutes. Participants were open to ask questions of the site coordinators before or after the test but not while it took place.

The test consisted of 15 short edited videos (<1 minute), which concentrated on the uNBI-DF features of the scar. At first the site coordinator used the first 5 videos to explain the key features they should look for (ie, training videos, 1 with recurrence and 4 without recurrence). The following 10 videos were then presented to the participants (ie, test videos, 1 with and 9 without recurrence), who were required to enter their prediction of each of the 3 key features into a form (Supplementary Figs. 1-3, available online at www.giejournal.org). The videos consisted of cases taken from our initial cohort and had a similar proportion of recurrence within scars as described by the literature on ER. The same test videos, but shuffled, were used 2 to 3 weeks after the initial test for intraobserver reliability evaluation. Only after the second test were the site coordinators authorized to disclose the correct diagnosis for each test video. The set of 20 rated videos per endoscopist was used for accuracy measures calculations.

In addition to responses for each video, the endoscopists were also required to provide information regarding their daily practice and experience. Information was collected on training (under training or finished training), area of interest within endoscopy (eg, luminal endoscopy, EUS), number of procedures performed,

frequency of colonoscopy procedures (at least once a week or not), routine use of NBI, and if the endoscopists considered himself or herself an expert in advanced endoscopic imaging. The 3 study phases (conceptualization, exploratory phase, and validation phase) are summarized in Figure 2.

Standard accuracy measures were used to describe the performance of each arm compared with histology. The McNemar test was used to compare HD-WLE and NBI-SCAR prediction in the exploratory phase. Comparison of proportions was performed using the N-1 chi-squared test. Inter-rater reliability was calculated with Fleiss' free-marginal kappa because there were no restrictions for distribution across categories.[12] Intrarater reliability was calculated using the chance-adjusted index Bennett S score, as opposed to Cohen's kappa, because of the high-agreement and low-kappa paradox.[13] Both inter-rater and intrarater reliability values were interpreted as follows: .0 to .2, slight agreement; .21 to .40, fair agreement; .41 to .60, moderate agreement; .61 to .80, substantial agreement; and .81 to 1.0, almost perfect or perfect agreement. The Wilson score method without continuity correction was used to calculate 95% confidence interval for proportions.[14]

RESULTS

One hundred scars from 82 patients were included in the study. Patient mean age was 67.9 years, and 53% were men. Ninety-five scars enabled diagnosis with high confidence, and 19 had recurrence. The initial histology of the lesions was high-grade dysplastic adenoma in 33% (n = 33), low-grade dysplastic adenoma in 55% (n = 55), dysplastic sessile serrated adenoma/polyp (SSA/P) in 5% (n = 5), and nondysplastic SSA/P in 7% (n = 7). From the 5 scars predicted with low confidence, the index polyp was nondysplastic SSA/P (1) and tubulovillous adenoma (4).

Overall, the NBI-SCAR classification presented 5 false positives and had achieved an overall accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 95.0%, 100%, 93.8%, 79.2%, and 100%, respectively. HD-WLE presented 5 false negatives and 2 false positives (accuracy = 93.0%, sensitivity = 73.7%, specificity = 97.5%, PPV = 87.5%, NPV = 94.1%). For diagnoses with high confidence, all accuracy measures were raised to 100% with the NBI-SCAR classification (Table 1). NBI-SCAR sensitivity was statistically different from that of HD-WLE ($P < .01$). The recurrence/residual polyps were all diminutive in size and successfully treated with cold snare/cold avulsion and snare tip soft coagulation.

In the validation phase, across all 6 sites 49 endoscopists were recruited. The baseline characteristics of endoscopists who participated in the validation phase can be found in Table 2. Only 1 center was not an academic center (Malaysia).

The results varied across centers and was lowest for the nonacademic center (Table 3). The inter-rater reliability for high-confidence diagnoses across centers was moderate (κ = .50; 95% confidence interval, .43-.58), and the average intrarater reliability was fair (average S = .36). Looking at the various subsets, the results for consultants (accuracy = 89.4%, sensitivity = 88.7%, specificity = 89.5%, PPV = 49.1%, NPV = 98.6%) were higher compared to trainee-level endoscopists (accuracy = 84.9%, sensitivity = 76.7%, specificity = 85.8%, PPV = 36.5%, NPV = 97.2%). All comparisons reached statistical significance ($p < 0.05$) except for specificity ($p = 0.09$) and NPV ($p = 0.13$). Optimal results were achieved for endoscopists who perform colonoscopies at least once a week and who are familiar with NBI, which consisted of 24 consultants and 4 trainees (Table 4). The inter-rater reliability for this subgroup across centers was substantial (κ = .61; 95% confidence interval, .51-.71), and the average intrarater reliability was moderate (average S = .52). The inter-rater reliability per center and the intraobserver reliability per endoscopist for high-confidence diagnoses can be found in the Supplementary Tables 1 and 2, respectively (available online at www.giejournal.org).

DISCUSSION

The systematic use of biopsy sampling for the evaluation of normal-looking scars has been proposed based on the concern of inconspicuous recurrence that can be missed by the endoscopist. This is illustrated by the study of Knabe et al[5] conducted from 2010 to 2013 that found a concerning 7% recurrence miss rate for normal-looking scars. However, in the last several years, technology has improved remarkably, and studies have demonstrated the potential for advanced endoscopic imaging to replace the more time-consuming histopathology assessment. For instance, according to Preservation and Incorporation of Valuable Endoscopic Innovations guidelines, advanced imaging could be used to replace histology for polyps with certain characteristics in some scenarios.[15] In addition to time-saving, using this type of strategy for scars could also lead to savings in costs related to both pathologic assessment and device usage.

A recent study from the EMR SCAR group[16] (ESCAPE trial) evaluated the use of HD-WLE and NBI with and without magnification for assessment of recurrence within post-ER scars. Similar to the present study, the EMR SCAR group also included an exploratory phase with real-time evaluation of scars and a validation phase that included an "offline" scar assessment by independent endoscopists. There are a few differences in our study compared with the ESCAPE trial[16]: (1) the suggestion of a standard classification to be used for

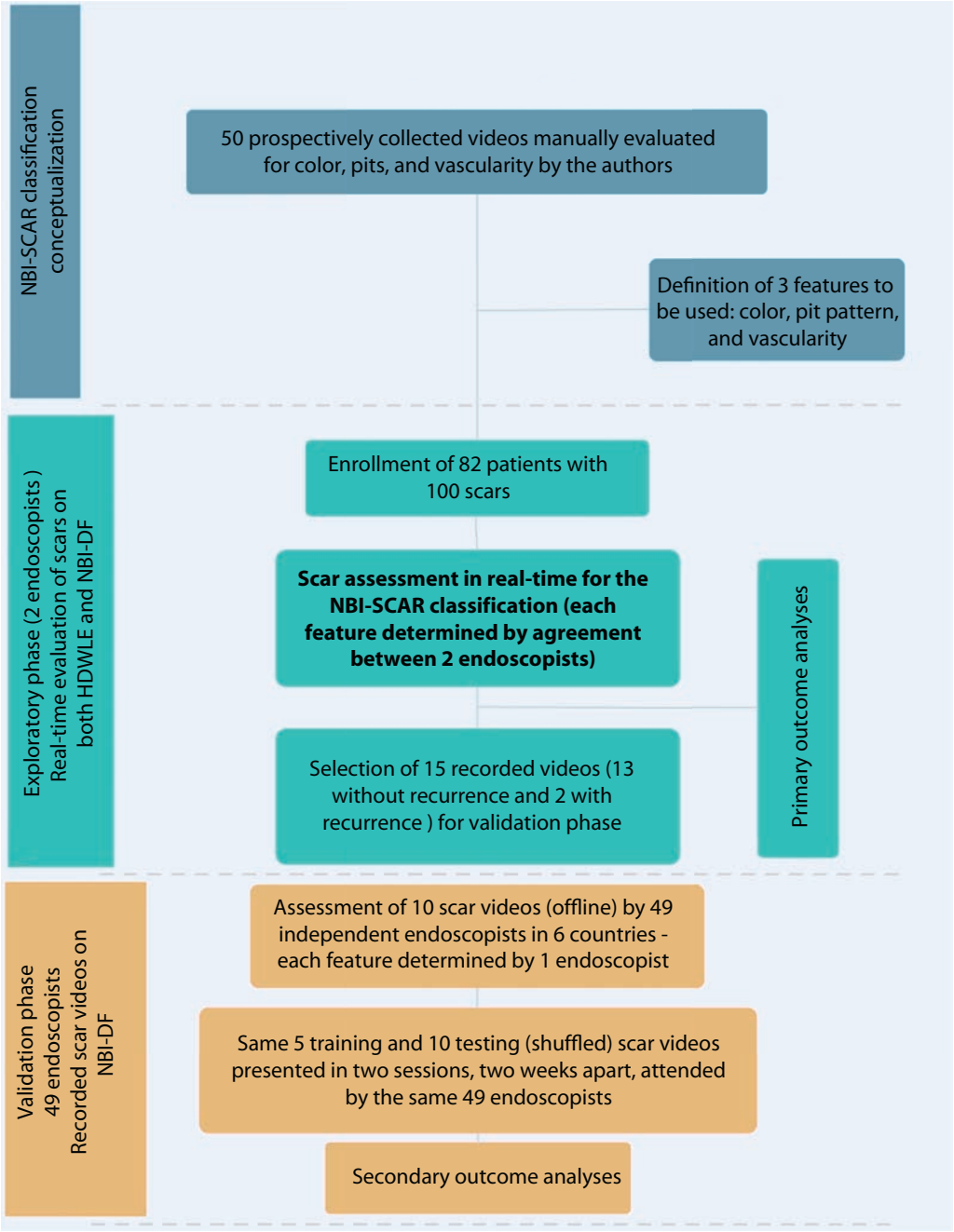

Figure 2. Study flowchart. *NBI-SCAR*, Narrow-band imaging for scar; *HD-WLE*, high-definition white-light endoscopy; *NBI-DF*, narrow-band imaging with dual focus.

assessment of scars, (2) the inclusion of not only experts in endoscopic imaging but also trainees and nonexperts, (3) the use of offline videos instead of still images for the validation phase, and (4) the scoring of the same scars after a period of time to assess the intrarater agreement.

One major problem that frequently occurs when aiming to use advanced endoscopic imaging to replace histologic assessment is the lack of consistency among proceduralists because of high interobserver variation.[17] To address this issue, several classifications have been proposed to standardize the method endoscopists use in evaluating colorectal polyp characteristics. In a not-too-dissimilar manner, this study proposes a standard classification with well-defined criteria to adopt advanced endoscopic imaging as a useful tool in the diagnosis of post-ER scars and recurrence at the scar site. This might facilitate the diagnosis for nonexperts and trainees.

By adopting the NBI-SCAR criteria in the exploratory phase, we were able to achieve an accuracy that is as good as histopathology for excluding neoplastic remnants even with a low-confidence diagnosis. Nevertheless, as

TABLE 1. Accuracy measures for NBI-SCAR and HD-WLE (exploratory phase)

	Arm	Accuracy	Sensitivity*	Specificity	Negative predictive value	Positive predictive value
Overall	NBI-SCAR	95.0 (88.8-97.9)	100 (96.3-100)	93.8 (87.3-97.1)	100 (96.3-100)	79.2 (70.2-86.0)
	HD-WLE	93.0 (86.3-96.6)	73.7 (64.3-81.3)	97.5 (92.3-99.2)	94.1 (87.7-97.3)	87.5 (79.6-92.6)
High confidence diagnoses	NBI-SCAR	100 (96.1-100)	100 (96.1-100)	100 (96.1-100)	100 (96.1-100)	100 (96.1-100)
	HD-WLE	94.7 (88.3-97.7)	73.7 (64.0-81.5)	100 (96.1-100)	93.8 (87.1-97.2)	100 (96.1-100)

Values are % (95% confidence interval).
NBI-SCAR, Narrow-band imaging for scar classification; *HD-WLE*, high-defintion white-light endoscopy.
*$P < .01$.

TABLE 2. Demographics per center (exploratory phase)

	United States	Japan	Brazil	Singapore	Malaysia	Australia
Total participants	12 (100)	12 (100)	13 (100)	7 (100)	2 (100)	3 (100)
Trainee-level	8 (66.7)	0 (0)	7 (53.8)	1 (14.3)	0 (0)	1 (33.3)
Consultant-level	4 (33.3)	12 (100)	6 (46.2)	6 (85.7)	2 (100)	2 (66.7)
Over 1000 procedures performed	7 (58.3)	10 (83.3)	13 (100)	3 (42.9)	2 (100)	1 (33.3)
Frequent colonoscopy	11 (91.7)	12 (100)	8 (61.5)	7 (100)	2 (100)	2 (66.7)
Routine use of NBI	4 (33.3)	12 (100)	8 (61.5)	5 (71.4)	0 (0)	2 (66.7)
Expert in NBI	1 (8.3)	11 (91.7)	3 (23.1)	1 (14.3)	0 (0)	0 (0)
Routine NBI/frequent colonoscopy	4 (33.3)	12 (100)	5 (38.5)	5 (71.4)	0 (0)	2 (66.7)

Values are n (%).
NBI, Narrow-band imaging.

TABLE 3. Summed high-confidence accuracy measures for NBI-SCAR (validation phase)

Country	Accuracy	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnosis possible	High-confidence diagnosis
Unites States (n = 12)	87.4 (82.6-91.0)	82.6 (77.3-86.9)	87.9 (83.2-91.4)	43.2 (37.1-49.5)	97.8 (95.1-99.0)	96.7 (93.6-98.3)	95.8 (92.5-97.7)
Japan (n = 12)	95.6 (92.2-97.6)	91.7 (87.5-94.6)	96.1 (92.8-97.9)	73.3 (67.4-78.5)	99.0 (96.8-99.7)	95.8 (92.5-97.7)	94.6 (91.0-96.8)
Brazil (n = 13)	78.8 (73.4-83.3)	73.9 (68.2-78.9)	79.3 (74.0-83.8)	27.9 (22.8-33.6)	96.6 (93.6-98.2)	93.8 (90.2-96.1)	90.8 (86.7-93.7)
Singapore (n = 7)	93.9 (88.6-96.8)	100 (97.3-100)	93.2 (87.8-96.3)	63.6 (55.4-71.1)	100 (97.3-100)	99.3 (96.1-99.9)	94.3 (89.2-97.1)
Malaysia (n = 2)	69.7 (54.3-81.7)	0 (0-8.76)	74.2 (59.0-85.2)	0 (0-8.76)	92.0 (79.5-97.2)	82.5 (68.1-91.3)	82.5 (68.1-91.3)
Australia (n = 3)	93.1 (83.8-97.2)	100 (94.0-100)	92.3 (82.7-96.8)	60.0 (47.4-71.4)	100 (94.0-100)	100 (94.0-100)	96.7 (88.7-99.1)

Values are % (95% confidence interval).
NBI-SCAR, Narrow-band imaging for scar classification.

with any highly sensitive test, false positives do appear (Fig. 3). However, in this scenario of surveillance colonoscopy post-ER, a false positive is easily dealt with by reverting back to the usual practice of taking samples for histopathology. In contrast, the presence of false negatives would be far more concerning in clinical practice. Fortunately, this was only found in the HD-WLE group (Fig. 4).

One concern that arises when using the NBI-SCAR classification is that it closely relates to the type 2 NBI International Colorectal Endoscopic classification and hence would only be able to predict typical adenoma and not SSA/P recurrence. Although only one of the recurrence cases was because of SSA/P recurrence, this was correctly diagnosed in the exploratory phase. Both recurrence cases included in the validation phase were adenoma recurrences. Further research evaluating the performance of the NBI-SCAR specifically for SSA/P recurrence is warranted.

The principles behind the adoption of uNBI-DF are not only to remove the light reflection cast on by the colonoscope but also to further enhance the mucosal surface

TABLE 4. High-confidence accuracy measures for NBI-SCAR (subset of frequent colonoscopy and routine use of NBI)

Country	Accuracy	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Diagnosis possible	High-confidence diagnosis
United States (n = 4)	88.5 (79.7-93.8)	100 (95.4-100)	87.1 (78.0-92.8)	47.1 (36.6-57.9)	100 (95.4-100)	98.8 (93.3-99.8)	97.5 (91.3-99.3)
Japan (n = 12)	95.6 (92.2-97.6)	91.7 (87.5-94.6)	96.1 (92.8-97.9)	73.3 (67.4-78.5)	99.0 (96.8-99.7)	95.8 (92.5-97.7)	94.6 (91.0-96.2)
Brazil (n = 5)	80.4 (71.6-87.0)	100 (96.3-100)	78.3 (69.3-85.3)	33.3 (24.8-43.0)	100 (96.3-100)	95.0 (88.8-97.9)	92.0 (85.0-95.9)
Singapore (n = 5)	92.7 (85.9-96.4)	100 (96.3-100)	91.9 (84.9-95.8)	58.8 (33.0-75.5)	100 (96.3-100)	100 (96.3-100)	96.0 (90.2-98.4)
Australia (n = 2)	95.0 (83.5-98.6)	100 (91.2-100)	94.4 (82.7-98.4)	66.7 (51.2-79.3)	100 (91.2-100)	100 (91.2-100)	100 (91.2-100)

Values are % (95% confidence interval).
NBI-SCAR, Narrow-band imaging for scar; *NBI*, narrow-band imaging.

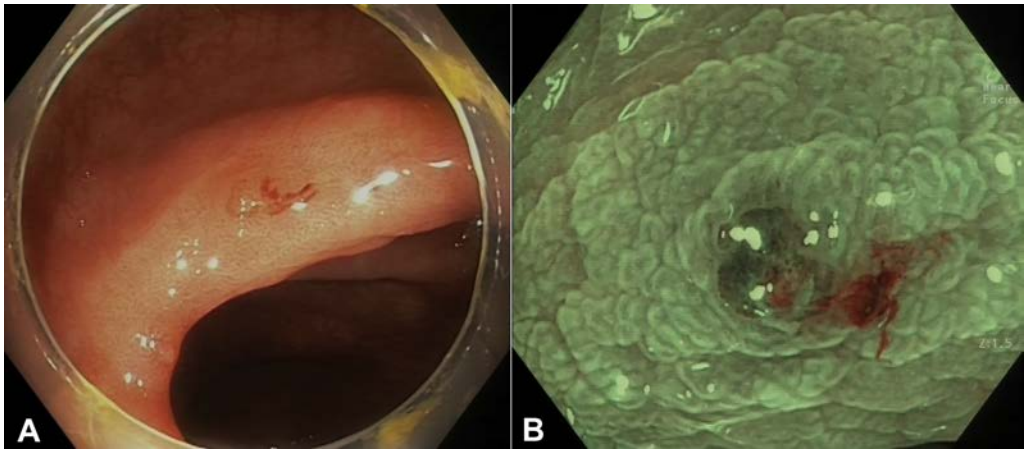

Figure 3. Example of a false positive with NBI-SCAR classification: (A) Scar on high-definition white-light endoscopy with small area of bleeding and redness at the center. (B) On narrow-band imaging area of interest presents with dark color, dense capillary network and unclear pits.

pattern. This provides the endoscopist with a magnified and unimpeded view that potentially minimizes the risk of missing neoplastic recurrence. From a more practical standpoint, however, although uNBI-DF appears to offer the best approach in scar site interrogation, this is not always feasible, especially when the area in question is in a difficult location. Thus, occasionally it can be technically challenging to maintain the underwater visualization long enough to properly evaluate the scar and/or for photo documentation. Therefore, although we believe it is useful to image the scar underwater and that uNBI-DF should be used whenever possible for investigating scars, NBI-DF without water immersion is satisfactory for NBI-SCAR as well. We strongly believe that the NBI-SCAR is a useful tool and should be simple enough to use with minimal training involved. Most colonoscopes are equipped with the NBI function, and no further equipment is required to use this technology. Nevertheless, further research is needed to confirm this postulation.

The comparison of imaging modalities in this study was limited to the exploratory phase and based on the dichotomy of HD-WLE and magnified NBI. We did not compare NBI versus NBI-DF. Although there is a possibility that NBI alone would be as accurate as NBI-DF in this study, it is likely that NBI with magnification was the best choice because it was shown to perform better than NBI alone for both polyps[18] and scars[16] in previous studies.

Our study had an unstructured approach rather than a structured methodology (eg, modified Delphi process) to identify which features to use in the classification. However, the NBI-SCAR features were derived from well-established colorectal polyp classifications such as the NBI International Colorectal Endoscopic classification (ie, color, pits, and vascular pattern). Because such features had already been validated as accurate predictors for neoplastic tissue by several studies, a more complicated approach for determining which features to use was not used. In addition, the NBI-SCAR study evaluated the combination of the 3 features but did not interrogate each individual feature for its contributions for the diagnosis of recurrence. Therefore, it is unclear how much each feature would have contributed to the results.

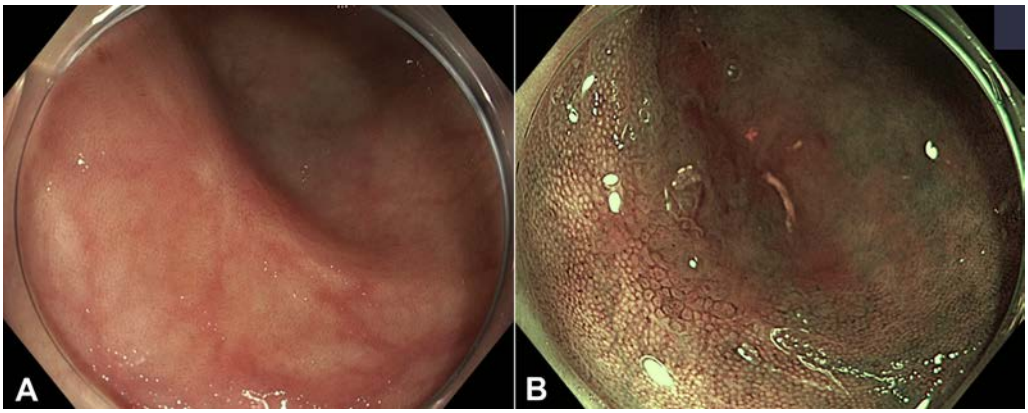

Figure 4. Example of a false negative with high-definition white-light endoscopy: (A) Scar on high-definition white-light endoscopy without signs of recurrence. (B) On narrow-band imaging, a central area with dark color, elongated and open pits, and dense capillary network is found.

The limitation of our study being conceptualized and evaluated within the same center was overcome with the validation phase. With this we were able to prove that a well-defined classification can lead to consistent results across different centers. In addition, bias from knowing the result from HD-WLE before the use of NBI during the real-time assessment of scars (exploratory phase) was mitigated when similar results were found in the validation phase. The validation of our classification among nonexperts in NBI and gastroenterology trainees suggests that it is easy and simple to learn. However, for optimal results, endoscopists must be familiar with using NBI and perform colonoscopies often. Another possible bias is related to follow-up colonoscopies on the same patients. Eleven of 100 scars included in the exploratory phase were re-evaluated during this period of the study. Although this could bias the endoscopists toward the results from the previous scar assessment, a simple strategy was adopted. During this period of the study, it was advised that for any follow-up colonoscopy, the endoscopists should only assess the endoscopy and pathology reports after they had imaged the scar.

In our center, the use of clips is mainly focused on treating adverse events rather than prophylactic use or to address the open wound per se. In our cohort, only 5 scars had through-the-scope clips used when the initial resection was performed. As highlighted by the ESCAPE and previous trials,[16,19] the use of clips might negatively influence accuracy through increased false positives. Therefore, in a center with a routine use of clips post-ER, the performance of the NBI-SCAR classification could be worse. However, the classification focuses on pits, vascularity, and color rather than surface features. Further studies addressing the use of the NBI-SCAR for this specific subset (scars with previous use of clips) are warranted for clarifying this question.

In conclusion, NBI-SCAR has a high sensitivity and NPV for excluding recurrence for endoscopists experienced in colonoscopy and NBI. In this setting, this approach may help to accurately evaluate or resect scars and potentially mitigate the burden of unnecessary biopsy sampling.

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REFERENCES

1. Hassan C, Quintero E, Dumonceau JM, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2013;45:842-51.
2. Tate DJ, Klein A, Desomer L, et al. Predicting adenoma recurrence after piecemeal colonic EMR is predictable: the Sydney EMR recurrence tool. Gastrointest Endosc 2017;85:647-56.
3. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. Endoscopy 2017;49:270-97.
4. Hwang JH, Konda V, Abu Dayyeh BK, et al. Endoscopic mucosal resection. Gastrointest Endosc 2015;82:215-26.
5. Knabe M, Pohl J, Gerges C, et al. Standardized long-term follow-up after endoscopic resection of large, nonpedunculated colorectal lesions: a prospective two-center study. Am J Gastroenterol 2013;109:183.
6. Yamada M, Saito Y, Takamaru H, et al. Long-term clinical outcomes of endoscopic submucosal dissection for colorectal neoplasms in 423 cases: a retrospective study. Endoscopy 2017;49:233-42.
7. Klein A, Tate DJ, Jayasekeran V, et al. Thermal ablation of mucosal defect margins reduces adenoma recurrence after colonic endoscopic mucosal resection. Gastroenterology 2019;156:604-13.
8. Desomer L, Tutticci N, Tate DJ, et al. A standardized imaging protocol is accurate in detecting recurrence after EMR. Gastrointest Endosc 2017;85:518-26.
9. Shahid MW, Buchner AM, Coron E, et al. Diagnostic accuracy of probe-based confocal laser endomicroscopy in detecting residual colorectal neoplasia after EMR: a prospective study. Gastrointest Endosc 2012;75:525-33.
10. Hewett DG, Kaltenbach T, Sano Y, et al. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. Gastroenterology 2012;143:599-607.
11. Hayashi N, Tanaka S, Hewett DG, et al. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the Narrow-Band

Imaging International Colorectal Endoscopic (NICE) classification. Gastrointest Endosc 2013;78:625-32.
12. Randolph J. Free-marginal multirater kappa (multirater κfree): an alternative to Fleiss fixed-marginal multirater kappa. Presented at the Joensuu University Learning and Instruction Symposium 2005, Joensuu, Finland, October 14-15, 2005. Available at: https://eric.ed.gov/?id=ED490661. Accessed May 1, 2019.
13. Warrens MJ. The effect of combining categories on Bennett, Alpert and Goldstein's S. Stat Method 2012;9:341-52.
14. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998;17:857-72.
15. Abu Dayyeh BK, Thosani N, Konda V, et al. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting real-time endoscopic assessment of the histology of diminutive colorectal polyps. Gastrointest Endosc 2015;81:502.e1-16.
16. Kandel P, Brand EC, Pelt J, et al. Endoscopic scar assessment after colorectal endoscopic mucosal resection scars: when is biopsy necessary (EMR Scar Assessment Project for Endoscope (ESCAPE) trial). Gut 2019;68:1633-41.
17. Rees CJ, Rajasekhar PT, Wilson A, et al. Narrow band imaging optical diagnosis of small colorectal polyps in routine clinical practice: the Detect Inspect Characterise Resect and Discard 2 (DISCARD 2) study. Gut 2017;66:887-95.
18. Iwatate M, Sano Y, Hattori S, et al. The addition of high magnifying endoscopy improves rates of high confidence optical diagnosis of colorectal polyps. Endosc Int Open 2015;3:E140-5.
19. Pellise M, Desomer L, Burgess NG, et al. The influence of clips on scars after EMR: clip artifact. Gastrointest Endosc 2016;83:608-16.

Abbreviations: ER, endoscopic resection; HD-WLE, high-definition white-light endoscopy; NBI, narrow-band imaging; NBI-SCAR, narrow-band imaging for scar; NPV, negative predictive value; PPV, positive predictive value; SSA/P, sessile serrated adenoma/polyp; uNBI-DF, underwater narrow-band imaging with dual focus; WLE, white-light endoscopy.

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NBI-SCAR questionnaire v.7

DATE:

THE UNIVERSITY of ADELAIDE

名古屋大学 NAGOYA UNIVERSITY

NBI-SCAR classification – Multicentre validation questionnaire

Dear colleague, thank you very much for participating in this study. NBI-SCAR is a classification based on advanced imaging that have demonstrated in our centre to be highly sensitive for excluding recurrence. It is based on three features evaluated on underwater NBI with magnification: colour, pit pattern and vascularity. If at least two concordant features are identified within the scar, it enables a diagnosis with high confidence.

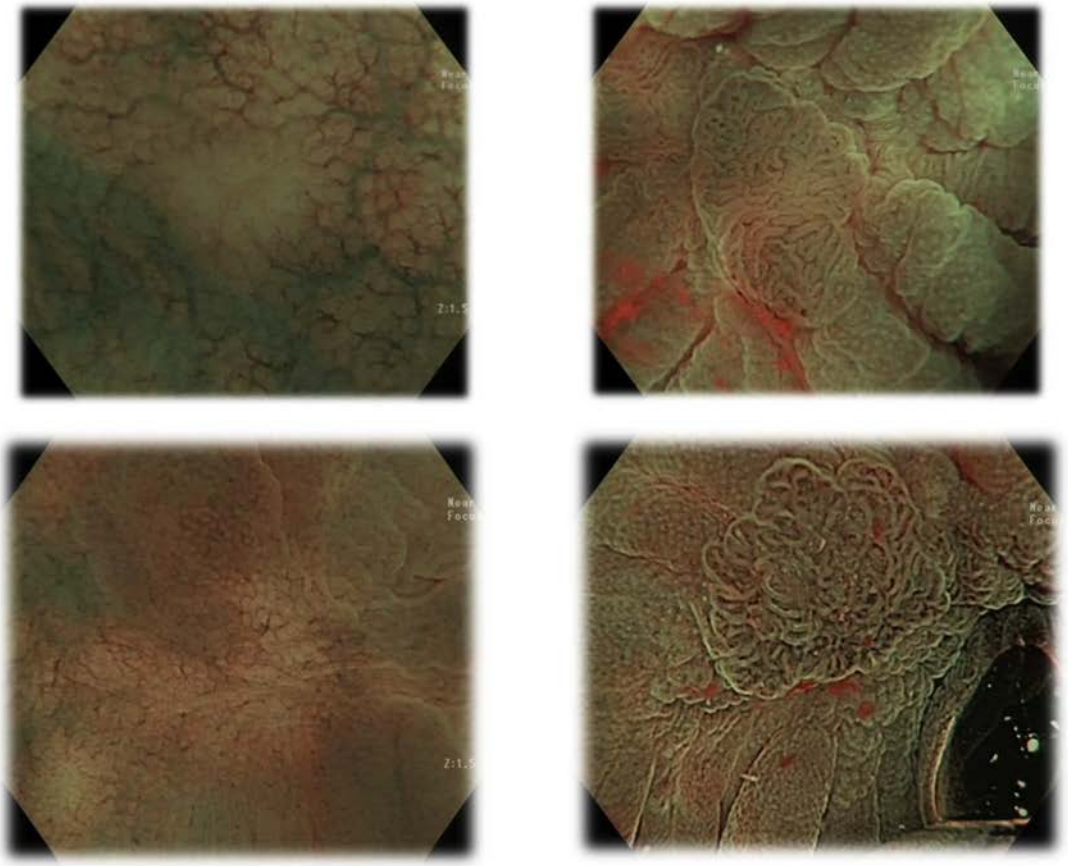
Please use the NBI-SCAR classification below as base for your responses regarding the videos that will be shown in the test. Finally, we would like to stress that all answers will be interpreted anonymously and for the purpose of this study only.

No recurrence

1. Whitish/pale appearance
2. Round and slightly larger pits
3. Irregular sparse vessels with no change in calibre

Recurrence

1. Dark brown colour
2. Elongated or branched pit pattern
3. Dense capillary pattern surrounding pits



Supplementary Figures 1-3. Validation forms.

NBI-SCAR questionnaire v.7

PLEASE CHOOSE ONLY ONE BOX PER FEATURE (3 PER VIDEO)

Video 1 – According to NBI-SCAR classification:

A. The scar colour is:
☐ whitish/pale ☐ dark/brown ☐ not discernible
B. The scar pit pattern is:
☐ round/slightly large ☐ elongated/branched ☐ no pit pattern
C. The scar vascularity is:
☐ sparse/irregular vessels ☐ dense capillaries surrounding pits ☐ no vascular pattern

Video 2 – According to NBI-SCAR classification, this scar:

A. The scar colour is:
☐ whitish/pale ☐ dark/brown ☐ not discernible
B. The scar pit pattern is:
☐ round/slightly large ☐ elongated/branched ☐ no pit pattern
C. The scar vascularity is:
☐ sparse/irregular vessels ☐ dense capillaries surrounding pits ☐ no vascular pattern

Video 3 – According to NBI-SCAR classification, this scar:

A. The scar colour is:
☐ whitish/pale ☐ dark/brown ☐ not discernible
B. The scar pit pattern is:
☐ round/slightly large ☐ elongated/branched ☐ no pit pattern
C. The scar vascularity is:
☐ sparse/irregular vessels ☐ dense capillaries surrounding pits ☐ no vascular pattern

Video 4 – According to NBI-SCAR classification, this scar:

A. The scar colour is:
☐ whitish/pale ☐ dark/brown ☐ not discernible
B. The scar pit pattern is:
☐ round/slightly large ☐ elongated/branched ☐ no pit pattern
C. The scar vascularity is:
☐ sparse/irregular vessels ☐ dense capillaries surrounding pits ☐ no vascular pattern

Video 5 – According to NBI-SCAR classification, this scar:

A. The scar colour is:
☐ whitish/pale ☐ dark/brown ☐ not discernible
B. The scar pit pattern is:
☐ round/slightly large ☐ elongated/branched ☐ no pit pattern
C. The scar vascularity is:
☐ sparse/irregular vessels ☐ dense capillaries surrounding pits ☐ no vascular pattern

Video 6 – According to NBI-SCAR classification, this scar:

A. The scar colour is:
☐ whitish/pale ☐ dark/brown ☐ not discernible
B. The scar pit pattern is:
☐ round/slightly large ☐ elongated/branched ☐ no pit pattern
C. The scar vascularity is:
☐ sparse/irregular vessels ☐ dense capillaries surrounding pits ☐ no vascular pattern

Video 7 – According to NBI-SCAR classification, this scar:

A. The scar colour is:
☐ whitish/pale ☐ dark/brown ☐ not discernible
B. The scar pit pattern is:

Supplementary Figures 1-3. Continued.

NBI-SCAR questionnaire v.7

☐ round/slightly large ☐ elongated/branched ☐ no pit pattern

C. The scar vascularity is:
☐ sparse/irregular vessels ☐ dense capillaries surrounding pits ☐ no vascular pattern

Video 8 – According to NBI-SCAR classification, this scar:

A. The scar colour is:
☐ whitish/pale ☐ dark/brown ☐ not discernible

B. The scar pit pattern is:
☐ round/slightly large ☐ elongated/branched ☐ no pit pattern

C. The scar vascularity is:
☐ sparse/irregular vessels ☐ dense capillaries surrounding pits ☐ no vascular pattern

Video 9 – According to NBI-SCAR classification, this scar:

A. The scar colour is:
☐ whitish/pale ☐ dark/brown ☐ not discernible

B. The scar pit pattern is:
☐ round/slightly large ☐ elongated/branched ☐ no pit pattern

C. The scar vascularity is:
☐ sparse/irregular vessels ☐ dense capillaries surrounding pits ☐ no vascular pattern

Video 10 – According to NBI-SCAR classification, this scar:

A. The scar colour is:
☐ whitish/pale ☐ dark/brown ☐ not discernible

B. The scar pit pattern is:
☐ round/slightly large ☐ elongated/branched ☐ no pit pattern

C. The scar vascularity is:
☐ sparse/irregular vessels ☐ dense capillaries surrounding pits ☐ no vascular pattern

Q1 - Which is your main area of interest? (Please choose only one)

☐ Upper endoscopy ☐ Colonoscopy ☐ Enteroscopy ☐ EUS ☐ ERCP ☐ Other_____

Q2 - Do you have more than 5 years of experience in gastrointestinal endoscopy after finishing endoscopy training?

☐ YES ☐ NO ☐ CURRENTLY UNDER ENDOSCOPY TRAINING

Q3 - Do you use to perform colonoscopies at least once a week?

☐ YES ☐ NO

Q4 - Do you routinely use NBI in your lists?

☐ YES ☐ NO

Q5 - Do you consider yourself experienced in advanced endoscopy imaging (e.g. accurate use of NBI and magnification for predicting mucosal dysplasia/polyp histology)?

☐ YES ☐ NO

Supplementary Figures 1-3. Continued.

SUPPLEMENTARY TABLE 1. Inter-rater reliability per center for high-confidence diagnoses

Center	Fleiss' free-marginal kappa
United States (n = 12)	.57
Japan (n = 12)	.67
Brazil (n = 13)	.32
Singapore (n = 7)	.64
Malaysia (n = 2)	.15
Australia (n = 3)	.65
Summed (n = 49)	.5

SUPPLEMENTARY TABLE 2. Intrarater reliability per endoscopist for high-confidence diagnoses

Intrarater reliability per endoscopist	Bennet S score	Routine NBI/frequent colonoscopy
United States rater 1	1	Yes
United States rater 2	.8	Yes
United States rater 3	.2	Yes
United States rater 4	.2	No
United States rater 5	.2	No
United States rater 6	0	No
United States rater 7	1	No
United States rater 8	.6	No
United States rater 9	.8	No
United States rater 10	.56	No
United States rater 11	0	No
United States rater 12	.4	Yes
Japan rater 1	.8	Yes
Japan rater 2	1	Yes
Japan rater 3	.2	Yes
Japan rater 4	.8	Yes
Japan rater 5	.78	Yes
Japan rater 6	.2	Yes
Japan rater 7	.8	Yes
Japan rater 8	1	Yes
Japan rater 9	.8	Yes
Japan rater 10	0	Yes
Japan rater 11	.4	Yes
Japan rater 12	.4	Yes
Brazil rater 1	−.2	Yes
Brazil rater 2	−.11	No
Brazil rater 3	−.2	Yes
Brazil rater 4	.4	Yes
Brazil rater 5	−.8	No
Brazil rater 6	0	No

(*continued on the next page*)

SUPPLEMENTARY TABLE 2. Continued

Intrarater reliability per endoscopist	Bennet S score	Routine NBI/frequent colonoscopy
Brazil rater 7	.4	No
Brazil rater 8	–.6	No
Brazil rater 9	.4	No
Brazil rater 10	.2	Yes
Brazil rater 11	.2	No
Brazil rater 12	.4	Yes
Brazil rater 13	–.56	No
Singapore rater 1	1	Yes
Singapore rater 2	.4	Yes
Singapore rater 3	.4	No
Singapore rater 4	.6	Yes
Singapore rater 5	.6	Yes
Singapore rater 6	.2	No
Singapore rater 7	.4	Yes
Malaysia rater 1	–.25	No
Malaysia rater 2	.11	No
Australia rater 1	.8	Yes
Australia rater 2	.6	Yes
Australia rater 3	.2	No

NBI, Narrow-band imaging.

Chapter 12

Conclusion

12.1 Discussion

Colorectal cancer is consistently found worldwide to be amongst the top five cancers in absolute years of life lost and cancer-related deaths, and its incidence has been increasing over the past decade[88-90]. On the other hand, the lethality of CRC is decreasing. This is likely related to bowel screening programs around the world and consequent CRC detection and treatment at an earlier stage[91-96].

The research reported in this thesis focussed on the use of endoscopy as a preventive health tool, concentrating on several aspects of premalignant polyps and early malignant colorectal cancer.

This thesis consists of one narrative review paper and nine original research papers. Although each study cohort had its unique characteristics, there is some overlap among the cohorts. A similar prospective cohort from the Lyell McEwin Hospital was used for the studies described in Chapters 3 and 7. A separate prospective cohort was used for the study described in Chapter 6. Another cohort (retrospective) from the Lyell McEwin Hospital, but with different extracted information, contributed to the studies described in Chapters 4 and 5.

Chapter 8 describes a study which used data from both the Nagoya University Hospital and Lyell McEwin Hospital databases. Each of the two studies conducted mainly in Japan consisted of a different cohort. Chapter 9 describes a prospective cohort and Chapter 10 a retrospective cohort from Nagoya University Hospital. Finally, a different prospective cohort (with few overlaps) from the Lyell McEwin Hospital was used in the study described in Chapter 11.

Firstly, factors associated with the detection of lesions were studied by reviewing the literature on several potential risk factors associated with CRC and polyps. There were discrepancies in the findings that can probably be attributed to sociocultural and geographical differences in the sample populations. In this context, the studies described in Chapters 3 and 4 examined patient- and endoscopist/hospital-related factors, respectively, and their association with colorectal lesions. The results add valuable information on factors associated with the detection of colorectal lesions, as such studies based on Australian data are currently limited. The results from these two studies are expected to guide future research and the development of potential health strategies relating to more efficient primary prevention of CRC.

To effectively maintain a screening strategy, quality assurance throughout the screening program is important. For colonoscopy screening, this means calculating quality measures such as ADR[97-100]. However, ADR measurement is often seen as cumbersome and unlikely to be

feasible in every endoscopy centre, given the need to follow-up all resected polyps, and calculating the ADR only when the final histology report is available. A method to address this issue has been proposed in the last few years, using PDR as a surrogate for ADR. This strategy has been studied mainly in the US and Europe [101, 102], with limited data from Australia. The use of an adenoma detection quotient (ADQ) (i.e. ADR/PDR) to predict ADR from PDR produces useful results, but can be influenced by local peculiarities, such as the population genotypical and phenotypical traits or the endoscopist's performance. Chapter 5 describes a study in which I calculated an ADQ from an Australian cohort and assessed the correlation of predicted and real ADR. Interestingly, the findings are similar to ADQs found in previous studies from abroad, corroborating that using PDR as a surrogate for ADR might be a feasible alternative strategy to directly calculating ADR.

A postulation could be made for the use of ADQ in clinical practice observing the following sequence: 1 - ADQ value should be confirmed through a few academic and non-academic centres throughout the country; 2 - once implemented, random audits once a year (e.g., in one academic and one non-academic centre) should be enough to monitor whether the quotient has been maintained or needs adjustment; 3 - if the ADQ is unchanged for some years, it might be possible to widen these intervals.

The limitations of the retrospective Australian cohort involved in these studies include the small numbers collected in the one-year period and obtaining data from a single centre. However, the retrospective cohort still provided relevant information illustrating locoregional peculiarities from Australia that can be further investigated.

Chapters 6 and 7 consist of studies looking at advanced imaging and its ability to predict the histology of colorectal lesions in real-time. An accurate endoscopic classification for colorectal lesions allows not only a more appropriate 'on the spot' treatment choice of a lesion, but also could enable the decision on the necessary follow-up immediately after the colonoscopy, as opposed to only after the histology results come back from a laboratory. In addition, cost-saving strategies, such as the resect-and-discard and detect-and-disregard proposed by ASGE could be used. Chapter 6 initially compared the use of the MS classification with the NICE classification.

Although the results of this randomised study have shown the benefits of using MS, this comparison was not appropriate for a subset of lesions, as NICE does not include SSA/Ps as a separate category. With the proposition of a new add-on classification by a group in the Netherlands[56] which could be used for this purpose, a more comprehensive comparison has been made possible. In addition, the newly developed classification from Japan named JNET showed promising results. In light of these developments, endoscopic classifications for colorectal lesions were further investigated in the study described in Chapter 7.

The research in the study reported in Chapter 7 compared the most comprehensive and current classifications being used around the world. Similarly to the randomised trial described in Chapter 6, the MS classification in this study was also shown to be superior to NICE plus WASP and JNET plus WASP. These results were further confirmed by a validation phase in a different endoscopy centre (Nagoya, Japan) and for both NBI and BLI virtual chromoendoscopy technologies. Although these results must be confirmed by research in other centres, our studies suggest that MS classification could be the best choice with either NBI or BLI for predicting the histology of colorectal lesions.

Our research found that MS was the most accurate classification when predicting colorectal lesions, albeit it being a five-type classification what might impede its widespread use. An adjunct that could assist with its use would be the use of artificial intelligence as an aid to the endoscopist. We therefore embarked upon the challenging task of developing a computer-aided diagnosis (CAD) system that would allow a prediction of histology as accurate as experts for all lesions included in the MS classification.

The study described in Chapter 8 consists of our successful conjoint effort with the School of Computer Science in developing this. After conceiving it based on learning solely from our Australian NBI dataset with good results, the CAD was further tested with NBI and BLI images from Japan. Surprisingly, even though the AI was trained only with NBI images, it achieved similar results not only for NBI but also for BLI. Therefore, our CAD system could lend an ‘expert's eye’ to any endoscopist, hopefully improving diagnosis and therefore treatment of colorectal lesions. The next step of translating this program into the endoscopy room is currently under discussion.

The limitations of the prospective Australian cohort involved in these studies include the small numbers of participants and having data from a single centre. These issues were partially addressed in the studies described in Chapters 7 and 8 with the use of images and input from Nagoya University. The studies have provided evidence for the first time on the comparison of classifications with the potential to characterise SSA/Ps; and on the use of a CAD trained with one imaging technology and used with a different technology for characterisation of colorectal lesions. The reproducibility of the CAD system results with data from Japan brings the use of AI one step closer to be implemented in the endoscopy suite for real cases in real time.

Distinct from endoscopic imaging, but still looking at differences between the different histology of colorectal lesions, another study was designed and carried out in our partner institution, Nagoya University. Chapter 9 describes the evaluation of differences in the mucosal microbiome between early and invasive colorectal cancers. The results show that several genera and species of bacteria are more abundant in one or the other group. This includes the bacteria *Fusobacterium nucleatum* (Fn), that has consistently been found

associated with colorectal cancer in the literature. These findings may allow strategies other than endoscopic imaging to be used for the prediction of histology (e.g. swabs with a rapid test for a specific Fn abundance threshold). In addition, if Fn is confirmed to be not only associated with advanced CRC but also contributing to its progression, manipulating its abundance (e.g. pre/probiotics) could be a strategy by which to delay or halt the progression of pre and early cancers to invasive cancers.

When extensive and/or locally advanced colorectal lesions are found, the current gold-standard is to treat them with advanced endoscopic resection (i.e. EMR or ESD). Specifically, the ESD technique has been shown to deliver the best outcomes in terms of R0 (i.e. free microscopic margins) and *en bloc* resections (i.e. lesion retrieved in one piece with macroscopic free margins). However, the ESD is often associated with higher complication rates and a more difficult learning curve when compared to EMR. Therefore, we examined the learning curve for colorectal ESD in a large cohort of procedures from Nagoya University Hospital; this is outlined in Chapter 10. The results demonstrated that although the learning curve slowly evolves in regard to speed of dissection, ESDs were safely and efficaciously performed by trainees. This information supports teaching hospitals and gastroenterological societies around the globe by proving that ESD can be adequately conducted by trainees with previous experience in advanced procedures.

Chapters 9 and 10 describe, respectively, studies based on a small prospective Japanese cohort and a large retrospective Japanese cohort. The limited numbers in the small cohort, due to elevated costs and limited time, were counterbalanced by a very effective manner of studying the microbiota (investigating the mucous cap rather than biopsies). On the other hand, the large numbers of the second cohort, even when diluted by the many endoscopists that performed ESD throughout the years, provided an impressive database when compared to data available from the West. Therefore, although there were limitations, the studies' results provide evidence that allows insights for further research and clinical practice.

Finally, Chapter 11 describes the development and validation of a new endoscopic classification for scars after endoscopic resection of colorectal lesions. The use of classifications for predicting histology of colorectal lesions dates from more than a decade ago, but no standard classification has been proposed for the prediction of histology from scars. Although some studies have suggested that the methodical evaluation of a scar with NBI is highly accurate for excluding recurrence, the lack of specific parameters and features to be evaluated make this strategy unlikely to be widely used.

With our study, we have conceived and validated the NBI-SCAR classification in six different countries (Australia, Malaysia, Singapore, Japan, United States and Brazil). The results suggest that when the endoscopists are familiar with advanced imaging technology (i.e. NBI) and

perform colonoscopies often, they are able to accurately exclude recurrence with the NBI-SCAR classification. This is true not only for experienced endoscopists but also for trainees. NBI-SCAR could potentially save time and costs associated with biopsies from scars predicted to return negative results, which consists of 80% to 95% of all scars. Therefore, this novel classification could be used in daily clinical practice as a cost-effective method for assessing colorectal mucosal scars.

12.2 Directions for future research

In addition to the potential contribution to clinical practice described in the previous sections, the research undertaken during my PhD could lead to future research, mostly looking to validate and advance our findings.

The main foci of this PhD were the primary and secondary prevention of CRC, given that the most effective way of minimising a disease's burden is to prevent it becoming established. For primary prevention, the identification and treatment of premalignant lesions are imperative. Despite having found factors associated with better detection and safe and effective treatment of colorectal lesions, these findings represent only a small sample of Australia's and Japan's larger health picture. Prospective, multicentre studies with large cohorts looking at the factors identified in Chapters 3 and 4 (e.g. time of the day, endoscopist specialty and diet) would be valuable as a next step. These studies should take into account locoregional differences and include SSA/Ps as premalignant colorectal lesions.

On a similar note, retrospective multicentre studies are needed for asserting quality measures in colonoscopy. The ADQ and SSA/P-DQ proposed in Chapter 5 are consistent with similar quotients found in the US and Europe, but their use in this current study confirms how limited the data from Australia and Japan are. Therefore, validation studies from other centres within Australia could potentially mount a case for the systematic use of ADQ and SSA/P-DQ for quality monitoring in colonoscopy. It is likely that in this specific case, the use of a retrospective design might be useful for avoiding the bias of an increased detection rate (due to endoscopist awareness).

The many endoscopic classifications available for characterising colorectal lesions at present make it difficult to choose a standard. Therefore, good quality evidence comparing the available systems is required for determining which to use. From the results described in Chapters 6 and 7, a possible next step would be to investigate through a multicentre randomised study the performance of classifications that can differentiate SSA/Ps. Research should include not only experts but also trainees and community endoscopists, as it is likely that these complex classifications will have variable results, depending on expertise.

As an alternative to dealing with the learning curve involved when acquiring the skill to accurately use comprehensive endoscopic classifications, a CAD was proposed in Chapter 8 to

aid the endoscopist in closing the gap between endoscopic and histologic diagnoses. Although already tested with different technologies and in different centres with reasonable results, the validation datasets were limited in size. A more sizeable and diverse validation dataset would enable researchers to draw more robust conclusions using our CAD system. In addition, the integration of the current CAD characterisation module with a detection module and finally to an interface with the endoscopy suite is paramount for the use of such technology in current practice. Another step that could be used to improve the applicability of the CAD for colorectal lesions in clinical practice is to attribute a confidence level to the diagnosis with further refinement of the algorithm.

Chapter 9 describes the different microbiota profile, specifically looking at the mucous cap on the colorectal lesion. The small numbers from this single centre study must be validated by studies from other centres from Japan and overseas, so consistency can be assessed. If consistent results are found, even if only within Japan, the potential for utilising the described differences in diagnosis and treatment would be the next step. The potential for diagnosis could be investigated by studying the relative abundance thresholds of specific bacteria in order to determine the invasiveness of CRCs. In addition, the potential for treatment could be evaluated when manipulating the microbiota of early CRCs in a prospective randomised study, and then assessing the mid and long-term outcomes after resection.

The safety and efficacy of colorectal ESDs described in Chapter 10 could be complemented by prospective studies from other centres. However, the limited number of ESDs performed outside Japan might be a deterrent. Therefore, multicentre prospective studies could be used for assessing whether similar safety and efficacy can be found outside Japan when trainees perform colorectal ESDs.

Finally, Chapter 11 focussed solely on tertiary prevention of CRC, proposing a method for sensitively detecting local recurrence in real-time during colonoscopy. Although prediction of scar histology through endoscopic imaging has been studied before, the NBI-SCAR classification is the first standard classification described for this end. Therefore, further multicentre prospective studies are required for validation of our findings. An optimal design would be to have proper training on the classifications with one of the centres involved in the index study, and then evaluate the performance of the NBI-SCAR classification with both experts and trainees in real-time diagnosis.

12.3 References for Chapter 12

88. Global Burden of Disease Cancer Collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. JAMA Oncology. 2019.

89. Gandomani H, Yousefi, S., Aghajani, M., Mohammadian-Hafshejani, A., Tarazoj, A., Pouyesh, V., & Salehiniya, H. Colorectal cancer in the world: incidence, mortality and risk factors. Biomedical Research and Therapy. 2017;4(10):10.

90. Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683-91. Epub 2016/01/29.

91. Lew JB, Feletto E, Wade S, et al. Benefits, harms and cost-effectiveness of cancer screening in Australia: an overview of modelling estimates. Public Health Research & Practice. 2019;29(2). Epub 2019/08/07.

92. Lew JB, St John DJB, Xu XM, et al. Long-term evaluation of benefits, harms, and cost-effectiveness of the National Bowel Cancer Screening Program in Australia: a modelling study. The Lancet Public health. 2017;2(7):e331-e40. Epub 2017/12/19.

93. Huang W, Liu G, Zhang X, et al. Cost-effectiveness of colorectal cancer screening protocols in urban Chinese populations. PLoS One. 2014;9(10):e109150. Epub 2014/10/07.

94. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. The American Journal of Gastroenterology. 2017;112(7):1016-30. Epub 2017/05/31.

95. Koo S, Neilson LJ, Von Wagner C, et al. The NHS Bowel Cancer Screening Program: current perspectives on strategies for improvement. Risk Management and Healthcare Policy. 2017;10:177-87. Epub 2017/12/23.

96. Jenkins MA, Ait Ouakrim D, Boussioutas A, et al. Revised Australian national guidelines for colorectal cancer screening: family history. Med J Aust. 2018;209(10):455-60. Epub 2018/10/26.

97. Kaminski MF, Thomas-Gibson S, Bugajski M, et al. Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) quality improvement initiative. Endoscopy. 2017;49(4):378-97. Epub 2017/03/08.

98. Hilsden RJ, Rose SM, Dube C, et al. Defining and applying locally relevant benchmarks for the adenoma detection rate. The American Journal of Gastroenterology. 2019;114(8):1315-21. Epub 2019/03/09.

99. Rees CJ, Thomas Gibson S, Rutter MD, et al. UK key performance indicators and quality assurance standards for colonoscopy. Gut. 2016;65(12):1923-9. Epub 2016/08/18.

100. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2017;86(1):18-33. Epub 2017/06/11.

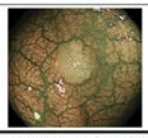
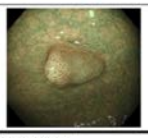
101. Schramm C, Scheller I, Franklin J, et al. Predicting ADR from PDR and individual adenoma-to-polyp-detection-rate ratio for screening and surveillance colonoscopies: a new approach to quality assessment. United European Gastroenterol J. 2017;5(5):742-9. Epub 2017/08/18.

102. Elhanafi S, Ortiz AM, Yarlagadda A, et al. Estimation of the adenoma detection rate from the polyp detection rate by using a conversion factor in a predominantly Hispanic population. J Clin Gastroenterol. 2015;49(7):589-93. Epub 2015/06/03.

Appendices

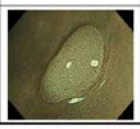
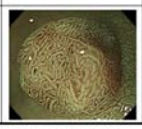
A.	Procedure **date** (d/m/y):	/ /
B.	**Gender**:	1 Male ☐ 2 Female ☐
C.	**Age** (in years)	
D.	Endoscopy **consultant and fellow/registrar**:	
E.	**Main indication** for performing the scope (choose one option only – if referred for resection of large polyp use the prior indication AND CHECK HERE ☐)	1 Age only ☐ 2 +ve FOB ☐ 4 1° relative polyps ☐ 5 1° relative bowel cancer ☐ 6 Other fam. Hx polyps ☐ 7 Other fam. Hx bowel ca. ☐ 8 Previous ER ☐ 9 Previous polyps ☐ 10 Previous bowel ca. ☐ 11 PR bleeding ☐ 12 Abdominal pain ☐ 13 Altered bowel habit ☐ 14 Iron deficiency anemia ☐ 15 Other ☐ _____
F.	Patient **post-colectomy?** Which type of surgery?	0 No ☐ 1 Yes ☐_____
G.	**BBPS?**	0-3 LC___TV___RC____
H.	**SCAR** of previous **EMR/ESD?** **Where?A**_____ **B**_____ **C**_____ (**can check multiple**)	0 No – ☐ 1 Yes – brown colouration ☐ 2 Yes – white colouration ☐ 3 Yes – elongated pits ☐ 4 Yes – round pits ☐ 5 Yes – vessels lining pits ☐ 6 Yes – irregular vessels ☐
I.	**WLE prediction?**	☐ No recurrence ☐ Recurrence
J.	**uNBI-DF prediction?**	☐ No recurrence ☐ Recurrence
K.	**Diverticulosis?**	☐RC ☐TV ☐LC ☐Sig ☐None

L.	**Polyp found?** (**if NO, end** of the form)	0 No ☐ 1 Yes ☐
M.	**Location and size** (size in mm, separate more than one polyp with slash and associate a letter: order from proximal to distal – e.g. A is polyp from caecum and B is polyp from transverse):	1 Rectum ☐ _____ 2 Sigmoid ☐_____ 3 Descending colon ☐____ 4 Splenic flexure ☐_____ 5 Transverse colon ☐____ 6 Hepatic flexure ☐_____ 7 Ascending colon ☐_____ 8 Caecum ☐_____
N.	**Paris'** classification: *Pedunculated* *Sub pedunculated* *Protruded >2.5mm* *Protruded <2.5mm* *Flat* *Depressed* *Excavated*	 1 Ip ☐ 2 Isp ☐ 3 Is or IIa+Is ☐ 2 IIa ☐ 3 IIb ☐ 4 IIc or IIa+c ☐ 5 III ☐
O.	**NICE** classification: 1 1 ☐ 2 2 ☐ 3 3 ☐ If **LST** (elevated > 10mm): 0 G-H ☐ 1 G-M ☐ 2 NG ☐	**Modified Sano** classification 1 I ☐ 2 IIo ☐ 3 II ☐ 4 IIIA ☐ 5 IIIB ☐ If **low confidence** diagnosis tick here ☐
P.	**JNET** classification	0 1 ☐ 2 2B ☐ 1 2A ☐ 3 3 ☐ If **low confidence** diagnosis tick here ☐
Q.	**Endoscopic features** suggestive of **SSA/P (for suspected HP and SSA/P only)?** (**can check multiple**)	0 None ☐ 1 Cloud-like surface ☐ 2 Inconspicuous margins ☐ 3 Debris on surface ☐ 4 Irregular shape ☐ 5 Open pit pattern ☐
R.	**VMV/DBV?**	0 No ☐ 1 Yes ☐

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (verify color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels may be present coursing across the lesion	Brown vessels surrounding white structures**	Has area(s) of disrupted or missing vessels
Surface pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular or branched white structures** surrounded by brown vessels	Amorphous or absent surface pattern
Most likely pathology	**Hyperplastic & sessile serrated polyp (SSP) *** **	**Adenoma****	**Deep submucosal invasive cancer**
Endoscopic image			

* Can be applied using colonoscopes with/ without optical (zoom) magnification
** These structures (regular or irregular) may represent the pits and the epithelium of the crypt opening.
*** In the WHO classification, sessile serrated polyp and sessile serrated adenoma are synonymous.
**** Type 2 consists of Vienna classification types 3, 4 and superficial 5 (all adenomas with either low or high grade dysplasia, or with superficial submucosal carcinoma). The presence of high grade dysplasia or superficial submucosal carcinoma may be suggested by an irregular vessel or surface pattern, and is often associated with atypical morphology (e.g., depressed area).

Figure 5 Narrow-band imaging (NBI) International Colorectal Endoscopic (NICE) classification.

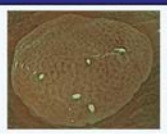
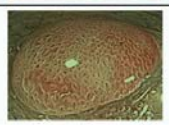
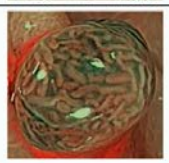
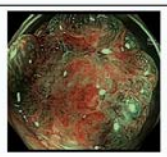
	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	• Invisible*1	• Regular caliber • Regular distribution (meshed/spiral pattern) *2	• Variable caliber • Irregular distribution	• Loose vessel areas • Interruption of thick vessels
Surface pattern	• Regular dark or white spots • Similar to surrounding normal mucosa	• Regular (tubular/branched/papillary)	• Irregular or obscure	• Amorphous areas
Most likely histology	Hyperplastic polyp/ Sessile serrated polyp	Low grade intramucosal neoplasia	High grade intramucosal neoplasia/ Shallow submucosal invasive cancer *3	Deep submucosal invasive cancer
Endoscopic image				

*1. If visible, the caliber in the lesion is similar to surrounding normal mucosa.
*2. Micro-vessels are often distributed in a punctate pattern and well-ordered reticular or spiral vessels may not be observed in depressed lesions.
*3. Deep submucosal invasive cancer may be included.

Figure 7 The Japan NBI Expert Team (JNET) classification.

S.	**Final endoscopic prediction** of polyp's type If **low confidence** diagnosis tick here ☐	1 Hyperplastic ☐ 2 TA ☐ 3 TVA ☐ 4 VA ☐ 5 Adenoma (LC for subtype) ☐ 6 SSA/P without dysplasia ☐ 7 SSA/P with dysplasia ☐ 8 TSA ☐ 9 Carcinoid ☐ 10 Hamartoma ☐ 11 Inflammatory ☐ 12 Superficial cancer ☐ 13 Invasive cancer ☐ 14 Other ☐ _____
T.	**Type of resection**: (for multiple polyps write in letters the order from proximal to distal – e.g. A is polyp from caecum and B is polyp from transverse)	1 Standard EMR ☐ → 2 Cold EMR ☐ → 3 ESD ☐ → 4 Hybrid ESD/EMR ☐ → For 1-4 = How many pieces:_____ 5 Hot snare ☐ 6 Cold snare ☐ 7 Hot biopsy ☐ 8 Forceps (cold) ☐ 9 Other ☐_____
U.	Snare Tip Soft Coagulation **(STSC)**	0 No ☐ 1 Yes – for EMR ☐ 2 Yes – for ESD ☐ 3 Yes – for scar ☐
V.	**Fellow involved** in *endoscopic resection* itself?	0 No ☐ 1 Yes – solely ☐ 2 Yes – mainly ☐ 3 Yes – minimally ☐

OBS:

MS Classification (predicted histology)	Description	Example
Type I (Hyperplastic polyp)	Pale, central brown dots or bland appearance + minute capillaries which may meander across polyp	
Type IIo (Sessile serrated adenoma)	Pink mucous cap ± wavy cloud like appearance ± brown 'open' round pits + capillaries which may meander across the polyp	
Type II (Tubular adenoma with low grade dysplasia)	Minimally branched cerebral surface + Brown, linear or oval capillary network present which surrounds white linear or oval pits	
Type IIIa (Tubular adenoma with high grade dysplasia/ Villous or Tubular villous adenoma/ Intramucosal cancer)	Remarkably branched villous/cerebral surface + Brown, high density capillary network with tortuosity, branching and lack of uniformity.	
Type IIIb (Invasive cancer)	Friable pale surface with avascular capillary network	

W.	Any complications or unusual procedures? (**if NO, end** of the form)	0 No ☐ 1 Yes, for complication ☐ 2 Yes, prophylactic clip for bleeding (no active bleeding) ☐ 3 Yes, prophylactic clip for perf (no through perforation) ☐
X.	Significant **bleeding <u>during procedure</u>** requiring treatment:	0 None ☐ 1 Clip(s) ☐ 2 Adrenaline injection ☐ 3 Coagrasper ☐ 4 STSC ☐ 5 Other thermal coagulation ☐
Y.	**Bleeding control**:	0 Not applicable ☐ 1 Controlled and placed prophylactic clip ☐ 2 Controlled and no further treatment required ☐ 3 Bleeding uncontrolled ☐ If so, outcome: _____
Z.	**Perforation** noted during procedure	0 No ☐ 1 Uncertain/Prophylactic clip ☐ 2 Yes ☐
AA.	**Treatment of perforation**	0 Not applicable or None ☐ 1 Clips ☐ 2 Laparascopic Surgery ☐ 3 Open Surgery ☐
AB.	**Significant pain** after procedure **requiring hospital admission**	0 No ☐ 1 Yes ☐
AC.	Significant **<u>post-procedure bleeding</u> (same day)** requiring repeat endoscopy?	0 No ☐ 1 Yes ☐
AD.	What **treatment** was used at repeat same day endoscopy for bleeding?	0 Not applicable or none ☐ 1 Clip(s) ☐ 2 Adrenaline injection ☐ 3 Coagrasper ☐ 4 Other thermal coagulation ☐ 5 Hemospray ☐ 4 Other ☐_____
AE.	**Overnight admission required post-procedure?**	0 No ☐ 1 Social reasons ☐ 2 Co-morbidities ☐ 2 Pain ☐ 3 Bleeding ☐ 4 Fever ☐ 5 Perforation ☐ 6 Large lesion (preventive) ☐ 7 Post-resection syndrome ☐ 8 Other reason ☐_____

DATE:

THE UNIVERSITY of ADELAIDE

STICKER HERE

PROSPECTIVE COLONIC POLYP COHORT – LYELL MCEWIN HOSPITAL AND NAGOYA UNIVERSITY HOSPITAL

Dear patient, thank you very much for participating in this study. It will help us to get a better understanding of colorectal polyps and cancer. I would like to ask you some questions that will be interpreted anonymously and for scientific purpose only.

Do you have diabetes (that require medicines such as metformin or glibenclamide)?	☐ YES ☐ NO
Do you regularly use Metformin (e.g. Diabex XR®, Diaformin XR®, Formet®, Glucophage®, Metex XR®)?	☐ YES ☐ NO
Do you use insulin?	☐ YES ☐ NO
Do you use aspirin every day?	☐ YES ☐ NO
Do you use any other blood thinners regularly? If yes which one and when did you last take it?	☐ YES_____ ☐ NO
Do you have hyperlipidaemia (high fat / cholesterol in the blood that require medicine such as statins or fibrates)?	☐ YES ☐ NO
Do you smoke at all?	☐ YES ☐ NO
If not, did you ever smoke? Stopped how many months ago?	☐ YES____months ☐ NO
Does any other person at your home currently smoke inside the house?	☐ YES ☐ NO
Do you drink alcohol at all?	☐ YES ☐ NO
Do you have more than 2 drinks a day if you are male and 1 drink a day if you are female?	☐ YES ☐ NO
If you do, which type of drink you usually have (e.g. wine, beer, sake)?	_____
Do you have more than two portions of fruit, vegetable, cereal or legume per day?	☐ YES ☐ NO
Do you have red meat (e.g. lamb, pork, beef) more than 3 meals per week?	☐ YES ☐ NO
Do you do more than 30 minutes of physical activity at least 3 times a week? Which type?	☐ YES_____ ☐ NO
What is your weight and height (approximately)?	_____kg _____metres/feet
How many first degree relatives have/had colorectal cancer (i.e. parent, siblings or children)? And second degree (e.g. cousins or grandparents)? At what age?	1st ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 or more___ 2nd ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 or more___
Why are you having this colonoscopy?	_____
Did you have any surgeries on your bowel (e.g. appendicectomy)? If yes why?	☐ YES_____ ☐ NO