Université de Montréal

Optimizing Endoscopic Strategies for Colorectal Cancer Screening

Improving colonoscopy effectiveness by optical, non-optical, and computer-based models

Par

Mahsa Taghiakbari

FACULTÉ DE MÉDECINE

Thèse présentée en vue de l'obtention du grade de Doctorat

en Sciences biomédicales, option Médecine expérimentale

Décembre 2022

Université de Montréal

Unité académique : Faculté de médecine

Cette thèse intitulée

Optimizing Endoscopic Strategies for Colorectal Cancer Screening

Improving colonoscopy effectiveness by optical, non-optical, and computer-based models

Présenté par

Mahsa Taghiakbari

A été évalué(e) par un jury composé des personnes suivantes

Dr. An Tang
Président-rapporteur

Dr. Daniel von Renteln
Directeur de recherche

Dr. Kevin Axel Waschke
Membre du jury

Dr. Neal Shahidi
Examinateur externe

Dr. Abraham Moishe Liberman
Représentant du doyen

Résumé

Introduction: Le cancer colorectal demeure un grave problème de santé publique au Canada. Les programmes de dépistage pourraient réduire l'incidence du cancer colorectal et la mortalité qui lui est associée. Une coloscopie de haute qualité est considérée comme un moyen rentable de prévenir le cancer en identifiant et en éliminant les lésions précurseurs du cancer. Bien que la coloscopie puisse servir de mesure préventive contre le cancer, la procédure peut imposer un fardeau supplémentaire à la santé publique par l'enlèvement et l'évaluation histologique de polypes colorectaux diminutifs et insignifiants, qui présentent un risque minime d'histologie avancée ou de cancer. La technologie de l'amélioration de l'image permettrait aux médecins de réséquer et de rejeter les polypes diminutifs ou de diagnostiquer et de laisser les polypes rectosigmoïdiens diminutifs sans examen histopathologique. Malgré la disponibilité de systèmes informatiques de caractérisation des polypes, la pratique du diagnostic optique reste limitée en raison de la crainte d'un mauvais diagnostic de cancer, d'une mauvaise surveillance des patients et des problèmes médico-légaux correspondants. Il est donc indispensable d'élaborer des stratégies alternatives de résection et d'élimination non optiques pour améliorer la précision et la sécurité du diagnostic optique et l'adapter à la pratique clinique. Ces stratégies doivent répondre à des critères cliniques simples et ne nécessitent pas de formation supplémentaire ni de dispositifs d'amélioration de l'image. De plus, la pratique sûre du diagnostic optique, la prise de décision appropriée concernant la technique de polypectomie ou l'intervalle de surveillance dépendent de l'estimation précise de la taille des polypes. La variabilité inter-endoscopistes dans la mesure de la taille des polypes exige le développement de méthodes fiables et validées pour augmenter la précision de la mesure de la taille. Une balance virtuelle intégrée à un endoscope haute définition est actuellement disponible pour le calcul automatique de la taille des polypes, mais sa faisabilité clinique n'a pas encore été établie. En dehors des points susmentionnés, une coloscopie de haute qualité nécessite l'examen complet de la muqueuse colique, ainsi que la visualisation de la valve iléocæcale et de l'orifice appendiculaire. À ce jour, aucune solution informatique n'a été capable d'assister les endoscopistes pendant les coloscopies en temps réel en détectant et en différenciant les points de repère cæcaux de façon automatique.

Objectifs: Les objectifs de cette thèse sont : 1) d'étudier l'effet de la limitation du diagnostic optique aux polypes de 1 à 3 mm sur la sécurité du diagnostic optique pour le traitement des

polypes diminutifs et l'acceptation par les endoscopistes de son utilisation dans les pratiques en temps réel tout en préservant ses potentiels de temps et de rentabilité ; 2) élaborer et examiner des stratégies non optiques de résection et d'élimination qui peuvent remplacer le diagnostic optique tout en offrant les mêmes possibilités d'économie de temps et d'argent ; 3) examiner la précision relative d'un endoscope à échelle virtuelle pour mesurer la taille des polypes ; 4) former, valider et tester un modèle d'intelligence artificielle qui peut prédire la complétude d'une procédure de coloscopie en identifiant les points de repère anatomiques du cæcum (c'est-à-dire la valve iléo-cæcale et l'orifice appendiculaire) et en les différenciant les uns des autres, des polypes et de la muqueuse normale.

Méthodes: Pour atteindre le premier objectif de cette thèse, une analyse post-hoc de trois études prospectives a été réalisée pour évaluer la proportion de patients chez lesquels des adénomes avancés ont été découverts et le diagnostic optique a entraîné une surveillance retardée dans trois groupes de taille de polypes : 1–3, 1–5, et 1–10 mm. Pour atteindre le second objectif de cette thèse, deux stratégies non optiques ont été développées et testées dans deux études prospectives: une stratégie de résection et d'élimination basée sur la localisation qui utilise la localisation anatomique des polypes pour classer les polypes du côlon en non-néoplasiques ou néoplasiques à faible risque et une stratégie de résection et d'élimination basée sur les polypes qui attribue des intervalles de surveillance en fonction du nombre et de la taille des polypes. Dans les trois études, la concordance de l'attribution d'intervalles de surveillance basée sur un diagnostic optique à haute confiance ou sur des stratégies non optiques avec les recommandations basées sur la pathologie, ainsi que la proportion d'examens pathologiques évités et la proportion de communications immédiates d'intervalles de surveillance, ont été évaluées. Le troisième objectif de cette thèse a été abordé par le biais d'une étude de faisabilité pilote prospective qui a utilisé la mesure de spécimens de polypes immédiatement après leur prélèvement, suite à une polypectomie par un pied à coulisse Vernier comme référence pour comparer la précision relative des mesures de la taille des polypes entre les endoscopistes et un endoscope à échelle virtuelle. Enfin, le quatrième objectif de cette thèse a été évalué par l'enregistrement et l'annotation prospective de vidéos de coloscopie. Des images non modifiées de polype, de valve iléo-caecale, d'orifice appendiculaire et de muqueuse normale ont été extraites et utilisées pour développer et tester un modèle de réseau neuronal convolutionnel profond pour classer les images pour les points de repère qu'elles contiennent.

Résultats: La réduction du seuil du diagnostic optique favoriserait la sécurité du diagnostic optique en diminuant de manière significative le risque d'écarter un polype avec une histologie avancée ou la mauvaise surveillance d'un patient avec de tels polypes. En outre, les stratégies non optiques de résection et d'élimination pourraient dépasser le critère de référence d'au moins 90% de concordance dans l'attribution des intervalles de surveillance post-polypectomie par rapport aux décisions basées sur l'évaluation pathologique. De plus, il a été démontré que l'endoscope à échelle virtuelle est plus précis que l'estimation visuelle de la taille des polypes en temps réel. Enfin, un modèle d'apprentissage profond s'est révélé très efficace pour détecter les repères cæcaux, les polypes et la muqueuse normale, à la fois individuellement et en combinaison.

Discussion: La prédiction histologique optique des polypes de 1 à 3 mm est une approche efficace pour améliorer la sécurité et la faisabilité de la stratégie de résection et d'écartement dans la pratique. Les approches non optiques de résection et d'élimination offrent également des alternatives viables au diagnostic optique lorsque les endoscopistes ne sont pas en mesure de répondre aux conditions de mise en œuvre systématique du diagnostic optique, ou lorsque la technologie d'amélioration de l'image n'est pas accessible. Les stratégies de résection et de rejet, qu'elles soient optiques ou non, pourraient réduire les coûts supplémentaires liés aux examens histopathologiques et faciliter la communication du prochain intervalle de surveillance le même jour que la coloscopie de référence. Un endoscope virtuel à échelle réduite faciliterait l'utilisation du diagnostic optique pour la détection des polypes diminutifs et permet une prise de décision appropriée pendant et après la coloscopie. Enfin, le modèle d'apprentissage profond peut être utile pour promouvoir et contrôler la qualité des coloscopies par la prédiction d'une coloscopie complète. Cette technologie peut être intégrée dans le cadre d'une plateforme de vérification et de génération de rapports qui élimine le besoin d'intervention humaine.

Conclusion: Les résultats présentés dans cette thèse contribueront à l'état actuel des connaissances dans la pratique de la coloscopie concernant les stratégies pour améliorer l'efficacité de la coloscopie dans la prévention du cancer colorectal. Cette étude fournira des indications précieuses pour les futurs chercheurs intéressés par le développement de méthodes efficaces de traitement des polypes colorectaux diminutifs. Le diagnostic optique nécessite une formation complémentaire et une mise en œuvre à l'aide de modules de caractérisation informatisés. En outre, malgré la lenteur de l'adoption des solutions informatiques dans la

pratique clinique, la coloscopie assistée par l'IA ouvrira la voie à la détection automatique, à la caractérisation et à la rédaction semi-automatique des rapports de procédure.

Mots-clés: Cancer colorectal; Endoscopie; Endoscope; Colonoscopie; Diagnostic optique; Adénome colorectal; Mesure de la taille; Apprentissage profond; Intelligence artificielle; Surveillance.

Abstract

Introduction: Colorectal cancer remains a critical public health concern in Canada. Screening programs could reduce the incidence of colorectal cancer and its associated mortality. A high-quality colonoscopy is appraised to be a cost-effective means of cancer prevention through identifying and removing cancer precursor lesions. Although colonoscopy can serve as a preventative measure against cancer, the procedure can impose an additional burden on the public health by removing and histologically evaluating insignificant diminutive colorectal polyps, which pose a minimal risk of advanced histology or cancer. The image-enhance technology would enable physicians to resect and discard diminutive polyps or diagnose and leave diminutive rectosigmoid polyps without histopathology examination. Despite the availability of computer-based polyp characterization systems, the practice of optical diagnosis remains limited due to the fear of cancer misdiagnosis, patient mismanagement, and the related medicolegal issues. Thus, alternative non-optical resection and discard strategies are imperative for improving the accuracy and safety of optical diagnosis for adaptation to clinical practice. These strategies should follow simple clinical criteria and do not require additional education or image enhanced devices. Furthermore, the safe practice of optical diagnosis, adequate decision-making regarding polypectomy technique, or surveillance interval depends on accurate polyp size estimation. The inter-endoscopist variability in polyp sizing necessitates the development of reliable and validated methods to enhance the accuracy of size measurement. A virtual scale integrated into a high-definition endoscope is currently available for automated polyp sizing, but its clinical feasibility has not yet been demonstrated. In addition to the points mentioned above, a high-quality colonoscopy requires the complete examination of the entire colonic mucosa, as well as the visualization of the ileocecal valve and appendiceal orifice. To date, no computer-based solution has been able to support endoscopists during live colonoscopies by automatically detecting and differentiating cecal landmarks.

Aims: The aims of this thesis are: 1) to investigate the effect of limiting optical diagnosis to polyps 1–3mm on the safety of optical diagnosis for the management of diminutive polyps and the acceptance of endoscopists for its use in real-time practices while preserving its time- and cost-effectiveness potentials; 2) to develop and examine non-optical resect and discard strategies that can replace optical diagnosis while offering the same time- and cost-saving potentials; 3) to

examine the relative accuracy of a virtual scale endoscope for measuring polyp size; 4) to train, validate, and test an artificial intelligence-empower model that can predict the completeness of a colonoscopy procedure by identifying cecal anatomical landmarks (i.e., ileocecal valve and appendiceal orifice) and differentiating them from one another, polyps, and normal mucosa.

Methods: To achieve the first aim of this thesis, a post-hoc analysis of three prospective studies was performed to evaluate the proportion of patients in which advanced adenomas were found and optical diagnosis resulted in delayed surveillance in three polyp size groups: 1–3, 1–5, and 1–10 mm. To achieve the second aim of this thesis, two non-optical strategies were developed and tested in two prospective studies: a location-based resect and discard strategy that uses anatomical polyp location to classify colon polyps into non-neoplastic or low-risk neoplastic and a polyp-based resect and discard strategy that assigns surveillance intervals based on polyp number and size. In all three studies, the agreement of assigning surveillance intervals based on high-confidence optical diagnosis or non-optical strategies with pathology-based recommendations, as well as the proportion of avoided pathology examinations and the proportion of immediate surveillance interval communications, was evaluated. The third aim of this thesis was addressed through a prospective pilot feasibility study that used the measurement of polyp specimens immediately after retrieving, following a polypectomy by a Vernier caliper as a reference to compare the relative accuracy of polyp size measurements between endoscopists and a virtual scale endoscope. Finally, the fourth aim of this thesis was assessed through prospective recording and annotation of colonoscopy videos. Unaltered images of polyp, ileocecal valve, appendiceal orifice and normal mucosa were extracted and used to develop and test a deep convolutional neural network model for classifying images for the containing landmarks.

Results: Reducing the threshold of optical diagnosis would promote the safety of optical diagnosis by significantly decreasing the risk of discarding a polyp with advanced histology or the mismanagement of a patient with such polyps. Additionally, the non-optical resect and discard strategies could surpass the benchmark of at least 90% agreement in the assignment of post-polypectomy surveillance intervals compared with decisions based on pathologic assessment. Moreover, the virtual scale endoscope was demonstrated to be more accurate than visual estimation of polyp size in real-time. Finally, a deep learning model proved to be highly effective in detecting cecal landmarks, polyps, and normal mucosa, both individually and in combination.

Discussion: Optical histology prediction of polyps 1–3 mm in size is an effective approach to enhance the safety and feasibility of resect and discard strategy in practice. Non-optical resect and discard approaches also offer feasible alternatives to optical diagnosis when endoscopists are unable to meet the conditions for routine implementation of optical diagnosis, or when image-enhanced technology is not accessible. Both optical and non-optical resect and discard strategies could reduce additional costs related to histopathology examinations and facilitate the communication of the next surveillance interval in the same day as the index colonoscopy. A virtual scale endoscope would facilitate the use of optical diagnosis for the detection of diminutive polyps and allows for appropriate decision-making during and after colonoscopy. Additionally, the deep learning model may be useful in promoting and monitoring the quality of colonoscopies through the prediction of a complete colonoscopy. This technology may be incorporated as part of a platform for auditing and report generation that eliminates the need for human intervention.

Conclusion: The results presented in this thesis will contribute to the current state of knowledge in colonoscopy practice regarding strategies for improving the efficacy of colonoscopy in the prevention of colorectal cancer. This study will provide valuable insights for future researchers interested in developing effective methods for treating diminutive colorectal polyps. Optical diagnosis requires further training and implementation using computer-based characterization modules. Furthermore, despite the slow adoption of computer-based solutions in clinical practice, AI-empowered colonoscopy will eventually pave the way for automatic detection, characterization, and semi-automated completion of procedure reports in the future.

Keywords: Colorectal cancer; Endoscopy; Endoscope; Colonoscopy; Optical diagnosis; Colorectal adenoma; Size measurement; Deep learning; Artificial intelligence; Surveillance.

Table of contents

Table list

Chapter 6

chapter 7

Chapter 8

Figure list

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

Supplementary table list

Supplementary figure list

Supplementary material

Chapter 7

List of acronyms and abbreviations

ADR: adenoma detection rate

AI: artificial intelligence

AO: appendiceal orifice

ASA: American Society of Anesthesiologists

ASGE: American Society for Gastrointestinal Endoscopy

ASGE PIVI: Gastrointestinal Endoscopy in its Preservation and Incorporation of Valuable endoscopic Innovations

BBPS: Boston Bowel Preparation Score

BSG: British Society of Gastroenterology

CER: Research Ethics Committee number

CIR: cecal intubation rate

CHUM: Centre Hospitalier de l'Université de Montréal

CI: confidence interval

CADx: Computer-based classification system

CNN: convolutional neural networks

CRCHUM: Centre de Recherche de Centre Hospitalier de l'Université de Montréal

DNN: deep neural networks

CRC: colorectal cancer

ESGE: European Society of Gastrointestinal Endoscopy

GEE: generalized estimating equations

HGD: high-grade dysplasia

ICV: ileocecal valve

IEE: image-enhanced endoscopy

IRB: institutional research board

JNET: Japan NBI Expert Team

LBRD: Location-Based Resect and Discard

mm: millimetre

n: number

NBI: narrow band imaging

NICE: NBI International Colorectal Endoscopic

NPV: negative predictive value

OD: optical diagnosis

P: P-value

PCCRC: post-colonoscopy colorectal cancers

PBRD: polyp-based resect and discard

PPV: positive predictive value

SSL/P/A: sessile serrated lesions/polyps/adenomas

SD: Standard Deviation

STARD: Standards for Reporting Diagnostic accuracy studies

USMSTF: US Multi-Society Task Force on Colorectal Cancer

VSE: virtual scale function for an endoscope

WASP: Workgroup on serrAted polypS and Polyposis

To Woman, Life, Freedom

À Femme, Vie, Liberté

Acknowledgment

First and foremost, I wish to express my sincerest gratitude to my supervisor, Dr. Daniel von Renteln for his constant guidance, support, patience and knowledge. His immense knowledge and plentiful experience have encouraged me in all the time of my academic research and daily life. I experienced a unique collaborative environment and I was offered tremendous freedom to work with multidisciplinary groups of experts to learn from them. Thank you for providing me with these opportunities.

My sincere thanks go to all the previous and current lab members without whom I would not have been able to complete this research. You made all research steps feel easy, fun, joyful and memorable. I appreciate all your help, and collaborations which made every step of my PhD experience a special one.

Last but not the least, I would like to appreciate all my family for standing by my side and giving me positive energy all the time, particularly my dear mother and father. Without their tremendous understanding and encouragement in the past few years, it would be impossible for me to complete my study; thank you all.

Introduction

1. Enhancing the Efficiency of Colonoscopy for Managing Diminutive Colorectal Polyps

Colorectal cancer (CRC) constitutes an important public health issue in Canada. It is estimated to be the fourth most commonly diagnosed cancer and the second and third leading cause of cancer-related deaths in men and women in 2022, respectively.[1] Colorectal polyps, the precursor lesions of CRC, can be classified according to their histopathological features or their clinico-pathological characteristics. According to histopathological features, colorectal polyps are classified into epithelial (conventional adenomas and serrated polyps), inflammatory, hamartomatous, stromal, lymphoid, malignant, and benign non-neoplastic mucosal polyps (i.e., hyperplastic and juvenile polyps).[2] Only a small number of polyps originate from the mucosa and pose a negligible clinical relevance.[3] Adenomatous polyps can further be categorized according to histologic features into three groups: tubular adenomas (over 80% of adenomatous polyps), villous adenomas (around 5-15% of adenomatous polyps), and tubulovillous adenomas (5-15% of adenomatous polyps). During the last three decades, serrated lesions have been proposed as a distinct polyp subtyped and vary in morphological patterns and molecular characteristics. They are classified into six different groups: microvesicular hyperplastic polyp, goblet cell hyperplastic polyp, sessile serrated polyp, sessile serrated polyps with dysplasia, traditional serrated adenoma, and unclassified serrated adenoma.[4] According to the clinico-pathological characteristics, polyps are classified as neoplastic and non-neoplastic. Neoplastic polyps include conventional adenomas (i.e., tubular, villous, tubulovillous), sessile serrated lesions, traditional serrated adenomas, dysplasia associated with chronic inflammatory bowel disease, neuroendocrine neoplasms, lymphomas, lymphomatoid polyposis (e.g., mantle cell lymphoma), leiomyomas, lipomas, perineuriomas or fibroblastic polyps, schwannomas, and inflammatory myofibroblastic tumors. On the other hand, non-neoplastic colorectal polyps encompass hyperplastic colonic mucosal polyps, polyps composed of granulation tissue, hamartoid polyps, heterotopia, lymphofollicular hyperplasia, and inflammatory fibroid polyps.[5] To classify an adenoma as advanced, it must meet one of the following criteria: (1) a size of 1 cm or larger as reported by the endoscopist, (2) histological evidence of villous architecture, or (3) the presence of high-grade dysplasia or invasive carcinoma.[6] Adenomas ≥10mm in size, regardless of histology,

are therefore classified as advanced adenomas and are associated with a more than 10-fold higher likelihood of advanced histology and high-grade dysplasia compared to polyps <10mm.[7-11]

Notable variations are observed in both the frequency and molecular characteristics of colorectal polyps, reflecting the distinct biologic milieu present along the colon and the varying conditions at the mucosal-luminal interface. Adenomatous polyps have a higher potential for malignant transformation compared to hyperplastic polyps, which are generally considered benign. The link between hyperplastic polyps and cancer has been less clear and remains a topic of ongoing research. Adenomas, particularly the tubular subtype, are more commonly found in the proximal colon whereas hyperplastic polyps tend to predominate in the distal colon and rectum.[12,13] Recent research suggests that adenomas in the proximal and distal colon exhibit distinct DNA methylation patterns, indicating that the process of carcinogenesis may differ depending on the location within the colon.[14,15] The prevalence of cancers displaying a CpG island methylator (CIMP) phenotype or a BRAF mutation progressively rises from the distal to the proximal colon.[16] The CIMP phenotype is often associated with hypermethylation of mismatch repair genes, leading to microsatellite instability. Consequently, the proportion of cancers with microsatellite instability is higher in the proximal colon.[17,18] Overall, individuals with proximal adenomas in the colon have a higher risk of developing metachronous adenomas compared to those with distal adenomas.[19-21] The risk is particularly elevated in individuals with multiple adenomas in the proximal colon.[21] Furthermore, proximal adenomas are more likely to lead to metachronous adenomas in the same region, while distal adenomas tend to recur in the distal colon.[21]

Polyps can be classified based on their size into different categories. Diminutive polyps are typically less than 5 mm in size, small polyps range from 6 to 9 mm, and large polyps are ≥10 mm in size. Accurate measurement and classification of polyps based on size play a vital role in guiding clinical decision-making, ensuring optimal patient care and reducing the risk of colorectal cancer development. The size of a polyp can influence the risk of malignancy and determine the need for further intervention. It also influences the determination of the post-polypectomy surveillance intervals, and decision on appropriate treatment options, such as polypectomy or endoscopic resection. The majority of polyps discovered during colonoscopy are diminutive, and they typically have a low likelihood of harboring advanced histology or developing into cancer.[7,22-24] A meta-analysis of four studies, involving a total of 20,562 subjects undergoing screening

colonoscopy, indicated that the prevalence of advanced neoplasia rises with larger polyp sizes. The prevalence rates varied from 0.9% in diminutive polyps to 73.5% in large polyps.[25] The optical diagnosis of diminutive polyps is based on the low probability of encountering advanced histology or cancer in the majority of diminutive polyps identified during colonoscopy.[7,22-24] By employing these strategies, the need for histopathology examinations is reduced, enabling prompt determination of surveillance intervals.[26]

CRC screening programs incur substantial costs due to the removal and histological assessment of insignificant diminutive polyps, accounting for approximately 80% of all detectable lesions.[23,27,28] Optical diagnosis has been recommended in 2011 by the American Society for Gastrointestinal Endoscopy in its Preservation and Incorporation of Valuable endoscopic Innovations (ASGE PIVI) initiative as a viable alternative strategy to replace histopathology examination of diminutive polyps.[29] This recommendation is in part driven by the fact that diminutive polyps harbor a negligible risk of advanced histology and cancer.[22]

Optical polyp diagnosis consists of two paradigms. Firstly, the “resect and discard” strategy involves removing all colorectal diminutive polyps and discarding them without histopathological evaluation, if no advanced histological features are predicted in optical polyp evaluation. This strategy can only be implemented routinely if the agreement between the determination of surveillance intervals based on high-confidence optical histology diagnosis of diminutive polyps, coupled with the pathology assessment of polyps >5 mm in size, and the pathology assessment of all identified polyps reaches ≥90%.[29] Secondly, the “diagnose and leave” allows for all hyperplastic rectosigmoid diminutive polyps being left in place without pathological histology assessment, only if optical histology prediction reaches ≥90% negative predictive value (NPV) for adenomatous histologic features.[29] Traditionally, conventional white light colonoscopy has been utilized for real-time and image-based differentiation of polyp histology during colonoscopy. However, its accuracy in distinguishing neoplastic from non-neoplastic colorectal polyps is relatively low, ranging from 59% to 84%.[30-33] Later, the utilization of chromoendoscopy, an originally Japanese-developed technique involving the administration of dyes like indigo carmine, demonstrated comparable accuracy to histopathology when combined with high-definition white light colonoscopy.[34] Chromoendoscopy offers a comprehensive assessment of colonic pit patterns known as Kudo classification.[35] This widely-employed classification system assigns Kudo patterns 1 and 2 to non-neoplastic lesions, while Kudo patterns 3s, 3L, and 4 are indicative of

neoplastic lesions, with Kudo pattern 5 suggesting submucosal invasion. High-definition colonoscopy coupled with chromoendoscopy demonstrates a high precision in optical diagnosis, achieving diagnostic accuracies ranging from 85% to 96%.[32,33,36-38] Nevertheless, the implementation of chromoendoscopy necessitates additional training, specialized equipment, substantial time investment, and a steep learning curve.[39] New advances in imaging technology have improved in-vivo optical histology classification of colorectal lesions, resulting in improved cost and time effectiveness of colonoscopy procedures. The distinction between adenomatous and hyperplastic polyps using these techniques relies on the evaluation of vascular and surface patterns (discussed in **Chapter 8**). A systematic review and meta-analysis conducted by the ASGE Technology Assessment Committee demonstrated that advanced image-enhanced endoscopy (IEE) (such as narrow-band imaging (NBI)) can be used to support the "diagnosis and leave" strategy of hyperplastic rectosigmoid diminutive polyps by exceeding a NPV threshold of 90% for adenomatous polyp histology (pooled NPV=91%; 95% CI=88-94).[40] Additionally, this estimate was higher among expert endoscopists, in academic centers, and with high-confidence optical diagnosis. Similarly, the agreement between the assignment of post-colonoscopy surveillance intervals using NBI-assisted optical diagnosis and pathology results could surpass the established threshold of agreement of at least 90% when performed by expert endoscopists, in academic centers, or with high confidence (all pooled agreements >90%).

Despite the potential for optical diagnosis to alter the management of diminutive polyps by reducing the number of required histopathology examinations and providing an immediate surveillance plan following a procedure, endoscopists routinely use histopathology for patients' clinical management to avoid misdiagnosis of cancer, clinical mismanagement (e.g., assigning incorrect surveillance intervals), or medical-legal issues.[26,41] Additionally, the implementation of this cost-saving strategy may be hindered by the unavailability of IEE technology (especially in community-based practices), extra time required for histology prediction and photo-documentation, a lack of expertise or knowledge regarding optical histology features or classification systems, and a lack of financial incentive due to the absence of remuneration to endoscopists. Clinical trials conducted in community-based endoscopy centers revealed suboptimal accuracy of endoscopists in optically predicting the histology of diminutive polyps.[42] Nevertheless, few studies have evaluated the accuracy of individual endoscopists practicing in community-based centers, suggesting that a didactic or computer-based training may improve diagnostic accuracy.[43] Currently, the "resect and discard" strategy is rarely employed in

endoscopic practice; only 13.7% of Canadian and 5.1% of American endoscopists believe that this procedure is feasible to be implemented.[41] In contrast, the "diagnose and leave" strategy has become standard practice for managing rectosigmoid diminutive polyps in the United States and probably in Canada.[44]

The current literature highlights the limitations of optical diagnosis, which might be overcome by artificial intelligence (AI) predictions of histology. AI solutions commonly use Convolutional Neural Networks (CNN) or Deep Neural Networks (DNN) to imitate human brain neural interconnections to analyse real-time images or videos.[45] Computer-based classification systems (CADx) have significantly contributed to improving the accuracy and feasibility of optical diagnosis among all endoscopists, regardless of their experience level. These systems are integrated in computer-based detection systems (CADe) with or without using IEE and are commercially available in Asia, Europe, and North America.[46-48] CADx suggests the most probable histology and a confidence level for the predicted histology[49-56], allowing the endoscopist to make an accurate optical diagnosis during the examination (**Figure 1**).

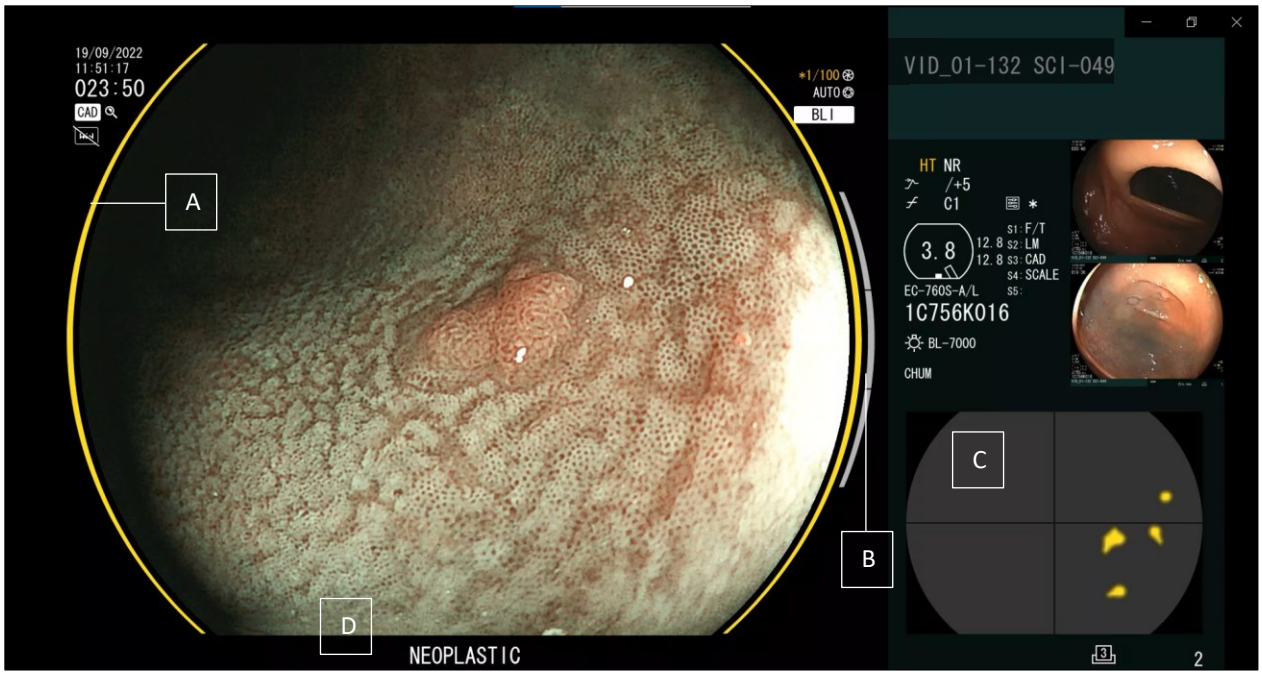


Figure 1 CADx module of the CAD-eye system; real-time polyp histology classification; A: visual assist circle: yellow if neoplastic characterization and green if hyperplastic characterization; B: status bar indicating the status of characterization analysis regarding to area suspected; C: position map indicating the position of the suspicious area; D: histology characterization results. Image courtesy Dr. Daniel von Renteln.

While CADx can fill the knowledge gap in optical diagnosis for non-expert endoscopists[57], there are some shortcomings that may hinder its broad real-time application. In contrast to popular IEE technology that is integrated into commercially available endoscopes, CADX is still an add-on device for existing high-definition standard or image-enhanced endoscopes. Therefore, due to the financial burden of purchasing an "extra" piece of equipment, its use may be limited to academic institutions with supplementary fundings.[57,58] Further, the remarkable accuracies of CADx systems are derived from AI algorithms that have been trained and tested using homogeneous and high-quality data collected by expert endoscopists in academic centers.[58,59] More specifically, these algorithms use selected clear colonoscopy images and videos that do not reflect the actual practice conditions, where positioning an endoscope to capture a polyp image or obtaining a clear polyp image can be difficult (e.g., inadequate bowel preparation, stool or blood in the field, challenging elongated or tortuous colon, or bowel movements), which may result in the “overfitting” of AI models that cannot achieve similar high accuracies when used in actual colonoscopy setting. Accordingly, it is crucial to evaluate the accuracy of CADx systems in multicenter and multi-endoscopist clinical trials in order to provide a testing ground for the effectiveness of CADx in meeting the ASGE PIVI optical diagnosis benchmarks.

1.1 Objectives

Because optical diagnosis is a cost- and time-saving approach and CADx systems still require improvement and validation through extensive clinical trials, the main objectives of this section are as follows:

1. to explore the effect of reducing the optical diagnosis threshold from 5 mm to 3 mm on the safety and efficacy of optical diagnosis;

2. to evaluate a location-based resect and discard model in which all diminutive polyps proximal to the sigmoid are considered adenomas, and all diminutive polyps in the rectosigmoid are considered hyperplastic;

3. to evaluate a polyp-based resect and discard model that assigns surveillance intervals based on polyp number and size.

With these objectives in mind, the present thesis aims to respond to the above-mentioned questions in **Chapters 1–3**.

Chapter 1 includes an article titled “What size cut-off level should be used to implement optical polyp diagnosis?” This article evaluated the use of different cut-off levels (1–3 mm, 1–5 mm, 1–10 mm) for optical diagnosis to determine the impact of reducing the optical diagnosis threshold on the safety and efficacy of optical diagnosis.

Chapter 2 includes an article titled “The location-based resect and discard strategy for diminutive colorectal polyps: A prospective clinical study.” This article proposed an alternative method to optical diagnosis that uses anatomical polyp location to classify colorectal polyps as either non-neoplastic or neoplastic.

Chapter 3 includes an article titled “Non-optical polyp-based resect and discard strategy: A prospective study.” In this article, another alternative to optical diagnosis was proposed to evaluate the feasibility of resect and discard strategy using polyp multiplicity and size.

1.2 Hypotheses

The following exploratory hypotheses were formulated:

Hypothesis 1-Chapter 1

1. A lower polyp size cut-off (e.g., 1–3 mm) is associated with a lower risk of misclassifying advanced neoplasia or cancer when using optical diagnosis while allowing for the forgoing of histopathology examination and the immediate communication of surveillance interval.

Hypotheses 2-Chapter 2

2.1 A location-based resect and discard model can reach a high agreement for assigning surveillance interval with pathology-based recommendations;

2.2 A location-based resect and discard model can differentiate neoplastic and non-neoplastic polyps with a high accuracy;

2.3 A location-based resect and discard model can reduce the number of required histopathology examinations and provide a high percentage of patients with a surveillance interval immediately following colonoscopy.

Hypotheses 3-Chapter 3

3.1 A polyp-based resect and discard model can reach a high agreement for assigning surveillance interval with pathology-based recommendations;

3.2 A polyp-based resect and discard model can reduce the number of required histopathology examinations and provide a high proportion of patients with surveillance interval immediately after colonoscopy.

2. Estimating the Accuracy of a Virtual Scale Endoscope (VSE) For Measuring Colorectal Polyp Size

The screening of CRC and prediction of the risk of future CRC following an index colonoscopy greatly depends on precise polyp size estimation. The development of appropriate strategies for improving the accuracy of polyp size measurement can be justified by four main arguments. First, the risk of advanced histology and malignancy correlates with polyp size.[60] Second, considering the increased risk of developing cancer in large polyps (≥10 mm), multiple guidelines, including the ASGE, adjust their recommendations for the next surveillance colonoscopy based on polyp multiplicity and size at a size cut-off of 10 mm regardless of the pathology subtype.[61,62] Therefore, it is expected that accurate size measurement would increase endoscopists' adherence to current guidelines for clinical decision-making on the next surveillance colonoscopy. Third, polyp size influences the choice of polypectomy technique and tools, which in turn would result in adequate polyp resection and reduction of interval cancer.[63-65] Last but not least, accurate polyp size measurement is crucial for the safe and effective implementation of optical diagnosis.

Although current research appears to validate the view that an accurate estimation of polyp size is essential for appropriate clinical decision-making, the absence of “gold standard” contradicts the determination of the most effective measurement strategy. The use of linear measuring probes, open biopsy forceps, graded caps, and graduated injection needles and snares has previously been demonstrated to yield accurate polyp sizing.[66-69] However, the subjective measurement of polyp size visually or by locating the polyp close to an open forceps or the tip of a closed snare (if a polypectomy is intended) has remained the preferable practice among endoscopists due to time, cost, and technical concerns associated with other methods. Despite expert endoscopists' best efforts, polyp size can commonly be underestimated or overestimated, leading to the recommendation of a longer or shorter surveillance interval. Accordingly, unnecessary screenings and histopathology examinations as well as the number of diagnosed CRC and the associated mortality would increase inappropriately.

Computerized assessments of polyp size may allow for more accurate measurement and are expected to become a standard feature in endoscope processors in the near future. Recently, Fujifilm has developed a novel virtual scale endoscope (VSE; SCALE EYE) that can superimpose a virtual linear or circular scale on an object during real-time colonoscopies (**Figure 3**).

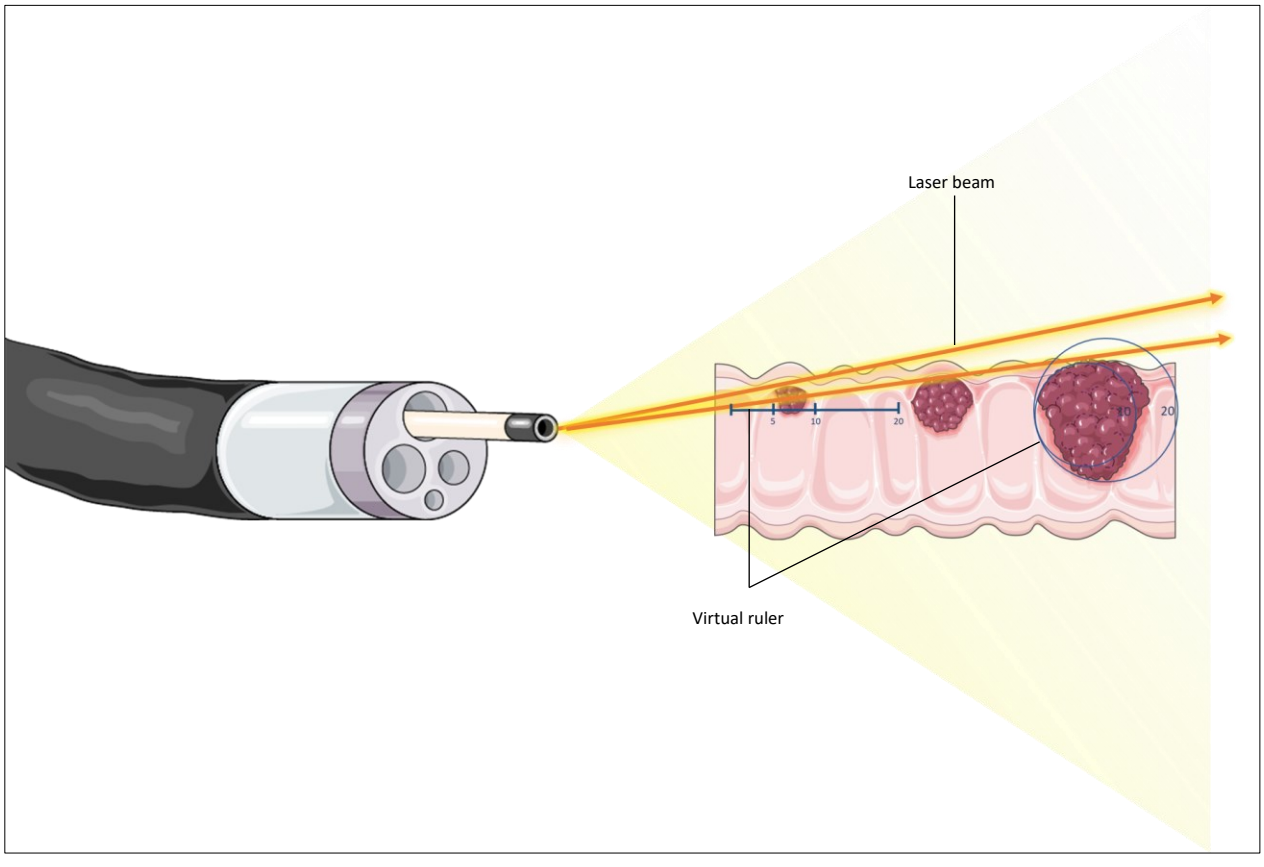


Figure 2 Virtual scale endoscope.

This virtual scale adjusts the length in real-time using a weak red laser beam emitted from the tip of the endoscope, according to the distance between the tip of the endoscope and the polyp, using the triangulation method for accurately estimating polyp size.[70] The effective range of the virtual scale is 4–30 mm. When the endoscope image sensor detects the laser spot positioned by the endoscopist on the left edge of a polyp, the distance from the tip of the endoscope to the polyp illuminated by the laser is calculated from the position of the laser spot. Consequently, the virtual scale will automatically overlay on the polyp. A dedicated software installed in a personal computer EX-1 (FUJIFILM Co., Tokyo, Japan) would measure this distance in real-time. The endoscope is part of the ELUXEO system (FUJIFILM Co., Tokyo, Japan) and supports image-enhanced modalities such as linked-color imaging (LCI) or blue-light imaging (BLI) to improve the detection and characterization of polyps. Therefore, endoscopists can conveniently switch the red laser on and off or use it along with the LCI or BLI. When an endoscopist pushes the button on the handle of the endoscope, the red laser will be emitted, and the virtual scale will appear as

a sky-blue bar or circle on the monitor. The scale bar will change the color to yellow if the size is out of range of the scale (<30 mm). According to a preliminary ex-vivo study, the virtual scale had a higher accuracy than biopsy forceps for measuring polyp size (84% versus 62.5%, p<0.001). This VSE, however, has never been evaluated and compared with subjective measurements in real-time.

2.1 Objectives

Given that an accurate, convenient, and reliable tool is necessary to ensure accuracy and consistency in polyp size measurement, the main objectives of this section are as follows:

1. to provide a comprehensive review on the efficacy of the available modalities and the recent technological advances for the measurement of polyp size;

2. to evaluate the accuracy of a newly developed computer-aided virtual scale endoscope for measuring polyp size in real-time and compare it with endoscopists' visual estimation of polyp size.

To this end, **Chapter 4** includes an article titled "Endoscopic size measurement of colorectal polyps: A review of methods and clinical implications." This chapter presents a comprehensive review of the current available measurement modalities, their associated strengths and limitations, and their clinical application.

Chapter 5 includes an article titled "Measuring size of smaller colorectal polyps using a virtual scale function during endoscopies." This article aims to examine the accuracy of the VSE and compare it with visual estimation of size using measurements obtained immediately after polyp excision by a Vernier caliper as a reference standard.

2.2 Hypothesis

Based on the information reviewed in **Chapter 4**, the following exploratory hypothesis was formulated:

<u>Hypothesis 1- Chapter 5</u>

1. An endoscope with an integrated virtual scale is an effective and feasible tool for estimating polyp size during a live colonoscopy, and its accuracy is superior to the visual estimation of size by endoscopists.

3. Development of An Artificial Intelligence Module to Detect and Discriminate Colonic Anatomical Landmarks (I.E., Appendiceal Orifice and Ileocecal Valve), Polyps and Normal Mucosa

Among available CRC prevention modalities, colonoscopy is of significant public health value due to its ability to prevent CRC by breaking the adenoma-carcinoma sequence through the detection and removal of premalignant colorectal lesions.[71] In recent years, a significant decline in CRC incidence has been attributed to improved detection and removal of CRC precursor lesions by colonoscopy procedures, as well as an increased participation of individuals in national screening programs.[71-73] A complete and high-quality colonoscopy that detects all precursor lesions and eliminates them completely will guarantee the effectiveness of screening programs in protecting against cancer.[73] The quality of colonoscopy is mostly determined by endoscopist-related factors (e.g., level of experience and technical skills of endoscopists) rather than patient-related factors. This is reflected in the incidence of post-colonoscopy colorectal cancers (PCCRC) or interval cancers. PCCRC develops after a normal or negative colonoscopy in which no cancer was detected, but probably one or more adenomas were missed, or detected adenomas were not removed completely.[74] The proportion of non-interval or de novo PCCRCs arising from rapidly progressing lesions is low.[75] Mutations in the mismatch repair genes are likely to contribute to the development of these cancers. It is estimated that approximately 30% of non-interval PCCRCs carry these mutations, and more than 80% of them are right-sided.[75,76] To minimize the impact of endoscopists' level of experience on the quality of colonoscopies and to ensure maximum protection against PCCRCs, the gastroenterology initiatives have developed several quality indicators that must be met by each endoscopist.[77-82] The primary and most clinically relevant surrogate measure of colonoscopy performance quality is the adenoma detection rate (ADR), which is directly associated with an improvement in long-term CRC prevention.[83] Every 1% increase in ADR results in a 3% decrease in the risk of developing CRC.[84] ADR is defined as the proportion of screening colonoscopies where at least one adenoma is found. The ASGE recommend a minimum ADR of 25% for all patients and sex-specific rates of 30% for men and 20% for women.

Computer-assisted detection systems (CADe) (**Figure 3**) provide real-time support to endoscopists by automatically detecting colorectal polyps during live procedures.

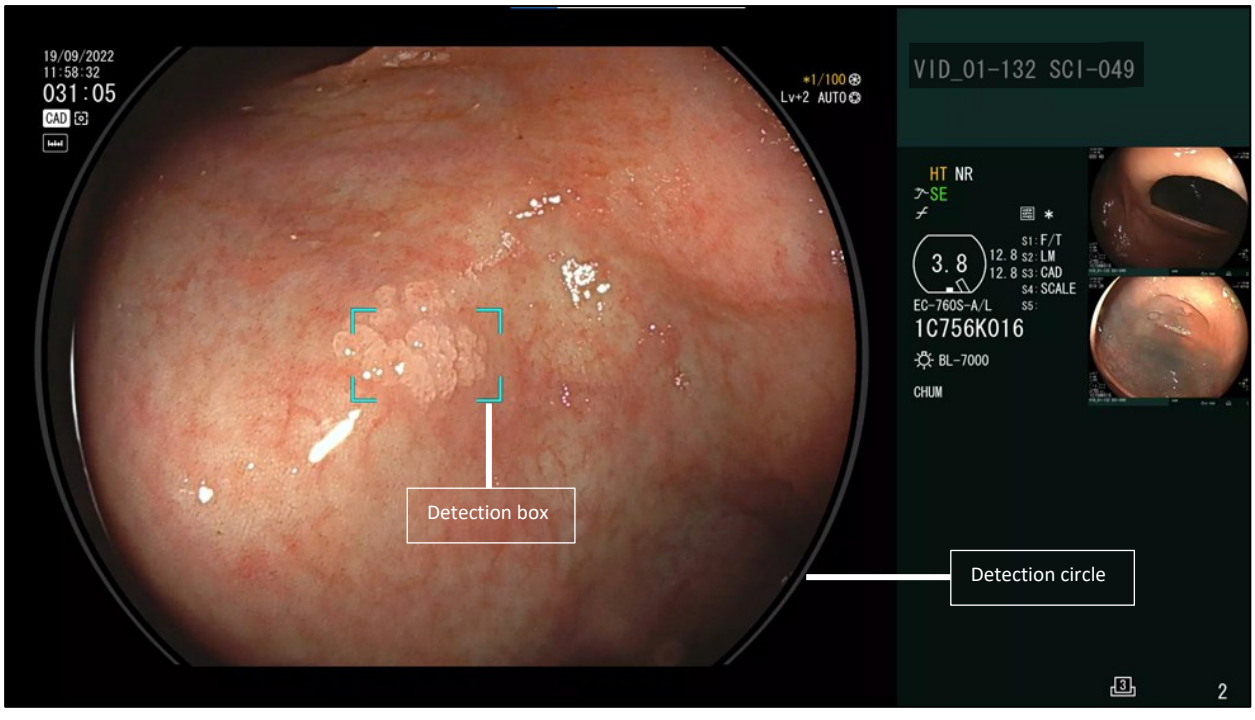


Figure 3 CADe module of the CAD-eye system; real-time polyp detection. Image courtesy Dr. Daniel von Renteln.

CADe programs are probably the most ideal adjunctive tool in protecting against PCCRC by producing up to 11% higher ADR compared to other ancillary techniques[51,85-87] and reducing adenoma miss rate by 50%[88,89]. These systems can reach a sensitivity of ≥90%, specificity of 63%-99%, and accuracy of >90%.[49,51,90-94]

Using either a standard or an AI-assisted colonoscopy, a high ADR can only be achieved through a complete examination of the entire colon. It is particularly important to perform a complete colonoscopy in order to detect a substantial fraction of adenomas that are located in the right colon.[78] The detection and photo-documentation of the ileocecal valve (ICV) and appendiceal orifice (AO) are critical metrics that indicate the cecum has been reached and colonoscopy is complete.[78] However, their detection is challenging due to variations in morphology, cecal distention and mobility, AO folded around the cecum, open or closed ICV, and occlusion of the visual field by stool. The development of computer-based solutions for assisting in the detection of key anatomical landmarks is highly advantageous. The currently available modules targeting the automatic detection of anatomical landmarks remained at their preliminary stages, have not been authorized for sale in Canada for clinical application because of insufficient clinical

validation and are confined to research settings due to deficiencies related to retrospective design, detection latency, and non-replicability under real-time conditions.[95]

3.1 Objectives

To date, no AI-assisted system has been developed that is capable of the co-detection of ICV, AO, and polyps and distinguishing them from one another and normal mucosa. Therefore, the main objectives in this section are as follows:

1. to assess the current status of computer-based detection, characterization, and quality assessment platforms, as well as to discuss the barriers to their widespread application in real-time practice;

2. to develop and test a deep convolutional neural network (DCNN) model that can automatically identify ICV and AO and differentiate these landmarks from normal mucosa and colorectal polyps.

Chapter 6 includes an article titled "Artificial intelligence-assisted colonoscopy: A review of current state of practice and research." Further, **Chapter 7** includes an article titled "Automated detection of anatomical landmarks during colonoscopy using a deep learning model." In this article, an AI DCNN-based model was proposed that could automatically recognize the cecal anatomical landmarks (i.e., ICV and AO) during a real-time colonoscopy and differentiate these landmarks from normal mucosa and colorectal polyps.

3.2 Hypothesis

Based on the information reviewed in **Chapter 6**, the following exploratory hypothesis was formulated:

<u>Hypothesis 1-Chapter 7</u>

1. An AI-based solution using a DCNN algorithm could automatically distinguish anatomical landmarks, such as the AO and ICV, from polyps and normal colon mucosa with high accuracy.

The last chapter (**Chapter 8**) of this thesis includes a discussion on the scope of the results and the possible ramifications of these findings within the context of the existing literature.

SECTION Ⅰ

Chapter 1 – Article 1: What Size Cut-Off Level Should Be Used to Implement Optical Polyp Diagnosis?

Chapter 2 – Article 2: The Location-Based Resect and Discard Strategy for Diminutive Colorectal Polyps: A Prospective Clinical Study

Chapter 3 – Article 3: Non-Optical Polyp-Based Resect and Discard Strategy: A Prospective Study

Chapter 1 – Article 1

What Size Cut-Off Level Should Be Used to Implement Optical Polyp Diagnosis?

Mahsa Taghiakbari,[1,2] Heiko Pohl,[3,4] Roupen Djinbachian,[2,5] Joseph C. Anderson,[3,4] Danny Metellus,[2,5] Alan Barkun,[6] Mickael Bouin,[2,7] and Daniel von Renteln[2,7]

[1]University of Montreal, Montreal, Quebec, Canada; [2]University of Montreal Hospital Research Center (CRCHUM), Montreal, Quebec, Canada; [3]Dartmouth Geisel School of Medicine, Hanover, New Hampshire, USA; [4]VA Medical Center, Whiter River Junction VT; [5]Division of Internal Medicine, University of Montreal Hospital Center (CHUM), Montreal, Quebec, Canada; [6]Division of Gastroenterology, McGill University Health Center, McGill University, Montreal, Quebec, Canada; and [7]Division of Gastroenterology, University of Montreal Hospital Center (CHUM), Montreal, Quebec, Canada

ABSTRACT

BACKGROUND AND AIMS: The risk of advanced pathology and potential mismanagement increases with polyp size while performing optical diagnosis. This study aimed to evaluate the proportion of patients undergoing inadequate surveillance intervals associated with different size cut-offs when using optical diagnosis.

PATIENT AND METHODS: In a post-hoc analysis of three prospective studies, the use of optical diagnosis was evaluated for three polyp size groups: 1–3, 1–5, and 1–10 mm. The primary outcome was the proportion of patients in which advanced adenomas were found and optical diagnosis resulted in delayed surveillance in each group. Secondary outcomes included agreements between surveillance intervals based on high-confidence optical diagnosis and pathology outcomes, reduction in histopathological examinations, and proportion of patients who could receive an immediate surveillance recommendation.

RESULTS: We included 3374 patients (7291 polyps ≤10 mm) undergoing complete colonoscopies (median age 66.0 years, 75.2% male, 29.6% for screening). The percentage of patients with advanced adenomas and either 2- or 7- year delayed surveillance intervals (n=79) was 3.8%, 15.2%, and 25.3% for size cut-offs of 1–3, 1–5, and 1–10 mm polyps, respectively (*P*<.0001). Surveillance interval agreements between pathology and optical diagnosis for the three groups were 97.2%, 95.5%, and 94.2%, respectively. Total reduction in pathology examinations for the three groups were 33.5%, 62.3%, and 78.2%, respectively.

CONCLUSION: A 3-mm cut-off for clinical implementation of optical diagnosis resulted in a very low risk of delayed management of advanced neoplasia while showing high surveillance interval agreement with pathology and a 1/3 reduction in overall required pathology examinations.

Keywords: Colonoscopy; Diminutive Polyps; Optical Diagnosis; Endoscopy; Screening; Surveillance.

1. Introduction

Small and diminutive colorectal polyps are the most common finding during colonoscopies.[1,2] Sending such polyps routinely to histopathology evaluation is costly and can likely be replaced by optical diagnosis.[1,3] However, current modalities for optical diagnosis cannot reliably distinguish between low- and high-risk dysplasia or provide an accurate prediction of sessile serrated lesions (SSL).[2,4-6] Thus, patients with advanced colorectal neoplasia might be at risk of inappropriate management and potential surveillance interval delays when undergoing optical diagnosis. As the risk of colorectal polyps harboring advanced pathology increases with size, a prudent implementation of optical diagnosis might ensure patient management's safety while confidently introducing optical diagnosis into routine clinical practice. Currently, optical diagnosis is typically used for diminutive (≤5 mm) colorectal polyps[7-10], although some authors have suggested expanding its application to polyps up to 10 mm.[11] It has even been suggested that pathology cannot be regarded as the reference standard for diagnosing polyps ≤3 mm, especially when a high-confidence optical diagnosis identifies an adenoma.[12] To date, no study has evaluated the impact of different size cut-offs on the appropriate management of patients undergoing optical diagnosis. We hypothesized that a lower polyp size cut-off (e.g., 1–3 mm) would be associated with a lower risk of misclassifying advanced neoplasia or even cancer when using optical diagnosis. The aim of this study was thus to evaluate how the application of different cut-offs (1–3 mm, 1–5 mm, 1–10 mm) would affect the safety and efficacy of optical diagnosis.

2. Methods

2.1 Study Design and Patients

This study is a post-hoc analysis of data from 3 prospective single-center studies (2 centers, 22 staff endoscopists, **Supplementary Table 1**), in which all patients underwent optical diagnosis for all polyps ≤10 mm found in the study cohorts.[13,14] The study population included patients aged 45–80 years undergoing complete elective colonoscopies at the Montréal University Hospital Center (CHUM)[13,14] and VA Medical Center White River Junction, VT. Exclusion criteria were known inflammatory bowel disease, active colitis, coagulopathy, familial polyposis syndrome, poor general health (American Society of Anesthesiologists class >3), and missing or unclear data on demographic or colonoscopy characteristics. Study outcomes are reported by following the

STARD (Standards for Reporting Diagnostic accuracy studies) recommendations.[15] Each study was approved by the institutional research board (IRB) (IRB number of the NORD study: 16.367 and OPTIVISTA study: 17.135, VA: 921356) and was registered at ClinicalTrials.gov (NCT04032912 and NCT03515343, respectively) for CHUM.

2.2 Study Procedures

Patients underwent standard bowel preparation. Participating endoscopists included board-certified gastroenterologists and fellows with various levels of expertise in optical diagnosis. During colonoscopies, endoscopists optically evaluated polyps ≤10 mm using different image-enhanced endoscopy (IEE) equipment: Optivista (1 and 2 Optivista Enhanced [OE] settings), i-Scan (1, 2, and 3 settings) (both Pentax Medical, Tokyo, Japan)[13,14,16], and narrow-band imaging (NBI, VA). Polyps were then classified based on the validated NBI International Colorectal Endoscopic (NICE) classification system as hyperplastic or adenoma in both centers. An additional assessment was performed to evaluate the serrated features (as in Sano classification) in polyps with hyperplastic classification, defined as the sessile serrated lesions (SSLs).[16] For each polyp, endoscopists also recorded whether the optical diagnosis was made with high or low confidence. A high level of confidence in optical diagnosis was assigned when a polyp had an endoscopic color, surface and/or vessel features associated with a specific type of histology in the NICE classification.[17] Common colonoscopy quality metrics such as cecal intubation, and quality of bowel preparation as well as size, location, and morphological characteristics based on the Paris classification of each polyp were also documented.[18] For analysis, polyps were stratified into three groups according to the endoscopic size: 1–3 mm, 1–5 mm, and 1–10 mm.

2.3 Definition of Advanced Polyp Histology

All 1–10 mm polyps with tubulovillous or villous histology, traditional serrated adenomas, any polyp histology with high-grade dysplasia, or cancer were considered as having advanced pathology.[5] Since the latest US Multi-Society Task Force on Colorectal Cancer (USMSTF) guideline recommends a shorter surveillance interval for patients with traditional serrated adenoma owing to the potential for malignancy, we considered traditional serrated adenoma as advanced adenoma.[5,19]

Histopathological assessment was available for all resected polyps. Qualified pathologists assessed polyp specimens according to current and institutional practice standards. Polyps were categorized as neoplastic (including adenomatous or sessile serrated lesions (SSL, large hyperplastic polyps ≥10 mm in size, SSL with dysplasia), and non-neoplastic (including hyperplastic polyps, inflammatory or mucosal prolapse, etc.).[20]

2.4 Surveillance Interval Calculation

Post-colonoscopy surveillance intervals based on optical diagnosis were determined for each patient based on a combination of the high-confidence optical pathology prediction, the histopathology results of polyps optically diagnosed with low confidence, and the histopathology outcomes of all other concomitant polyps. Poor bowel preparation and positive family history of colorectal cancer (CRC) were considered in final decisions on surveillance intervals. The reference standard surveillance interval was based on histopathological outcomes using the most recent (2020) USMSTF guideline.[2] Therefore, four different possible surveillance intervals were assigned to the patients: one based on actual histopathology outcomes, and three based on high-confidence optical pathology prediction using cut-offs of 1–3 mm, 1–5 mm, and 1–10 mm coupled with the histopathology reports of polyps with the low-confidence optical diagnosis.

2.5 Study Outcomes

The primary outcome was the proportion of patients for whom a polyp with advanced pathology undergoing optical diagnosis was misdiagnosed as a non-advanced or non-neoplastic polyp, resulting in an inappropriately delayed follow-up of either 2 or 7 years for those patients. This outcome was determined for each of the polyp size groups (1–3 mm, 1–5 mm, and 1–10 mm) in an attempt at determining the optimal size threshold for safe implementation of optical diagnosis. Thus, we calculated 1) the proportion of polyps with advanced pathology in each size group, and 2) the proportion of patients with advanced polyps who would have been assigned a delayed follow-up based on the NICE classification system.

Secondary outcomes included the agreements between surveillance intervals based on the optical diagnosis of polyps of the three size groups and the pathology-based recommendations. Other secondary outcomes were the diagnostic properties of optical prediction for neoplastic

rectosigmoid polyps, including accuracy, sensitivity, specificity, positive predictive value, and negative predictive value (NPV). The proportion of the reduction in histopathology examinations and the proportion of patients who could have received an immediate surveillance recommendation were also calculated for each of the three size cut-offs.

2.6 Statistical Analyses

Continuous variables are presented as means (and standard deviations) or medians (and ranges), as appropriate. Categorical variables are presented as proportions with 95% confidence intervals (CIs).

The diagnostic characteristics of optical diagnosis were calculated by sub-stratifying polyps into hyperplastic polyps and adenomas (excluding SSLs) within each of the three polyp size groups. The reduction in pathology examinations was calculated for: a) the reference standard – the number of polyps sent for histopathology evaluation divided by the total number of polyps; b) optical diagnosis – the number of polyps 1–3 mm, 1–5 mm, and 1–10 mm, respectively, optically diagnosed with high confidence divided by the total number of polyps. The proportion of patients who could have received immediate surveillance interval recommendations was calculated for: a) reference standard – the total number of patients without polyp identification during colonoscopy (normal colonoscopy) divided by the total number of patients; b) optical diagnosis – the sum of all patients without any polyps (normal colonoscopy) and patients with only polyps 1–3 mm, 1–5 mm, and 1–10 mm, respectively, optically diagnosed with high confidence divided by the total number of patients.

Comparing 1–3mm polyps to 4-5 mm polyps would introduce bias related to the size estimation by the endoscopists and histology determination by the pathologists. Therefore, the polyp size groups were partially overlapping, and observations from individuals tend to be correlated. To compare the proportions of outcomes of interest using different size cut-offs, we used Generalized Linear Models (i.e., binomial regressions) and a logit link to analyze all correlated errors and population-averaged estimates. To allow for within-subject observations that are equally correlated, we used an exchangeable working correlation matrix with robust standard errors. Hence, the separate regression models were fitted for our primary outcomes. The complete statistical methods have been explained in **(Supplementary Table 7**). The surveillance

interval agreements between optical diagnosis for different polyp size cut-offs and pathology were calculated for both the whole cohort of patients and the cohort of patients for whom optical diagnosis could have changed the recommended next colonoscopy (e.g., excluding patients with normal colonoscopy, polyps ≥10 mm in size, and poor bowel preparation). The agreements between the surveillance intervals were compared between the different size cut-offs using Cohens Kappa-Fleiss adjusted standard error.[21,22] Moreover, the proportions of correct and incorrect (shorter or longer) surveillance intervals using optical diagnosis were calculated for three size groups.

All point estimates are presented with 95% CIs and a p-value <0.05 was considered to indicate statistical significance. SPSS version 26.0 (IBM Corp., Armonk, New York, USA) and MedCalc Version 19.4 (MedCalc Software, Ostend, Belgium) were used for analyses.

3. Results

3.1 Patient, Procedure, and Polyp Characteristics

During the study period, 3921 patients underwent colonoscopy, and 3374 met the inclusion criteria and were included in the final analysis (**Supplementary Figure 1**). The median age of patients was 66 years, and 75.2% were male. Nearly a third (29.6%) of colonoscopies were performed for screening. Details of patient and colonoscopy characteristics are presented in **Table 1**. During colonoscopies, 5906 polyps 1–5mm in size and 1385 polyps 6–10 mm in size (total 1–10 mm polyps=7291) were detected. Among polyps sized 1–3 mm, 1–5 mm, and 1–10 mm with optical polyp evaluation, 2588/3212 (79.0%), 4813/5783 (81.5%), and 6033/7142 (82.7%), respectively, were diagnosed with high confidence. Polyp characteristics are presented in **Table 2**.

3.2 Proportion of Polyps with Advanced Pathology in the Respective Groups

Among polyp sized 1–3 mm, 1–5 mm, and 1–10 mm, 0.5%, 0.6%, and 1.2% of polyps, respectively, were found to have advanced pathology. Significant differences were noted in advanced histopathology proportions when comparing the 1–3 mm group versus 1–10 mm group and 1–5mm versus 1–10 mm groups, **Supplementary Table 2 and Table 7**).

3.3 Primary Outcome

When using optical diagnosis for polyps 1–3 mm, 1–5 mm, and 1–10 mm, the number of patients with advanced adenomas undergoing optical polyp diagnosis (n=79) resulting in delayed surveillances of either 2- or 7-years would have been 3 (3.8%), 12 (15.2%), and 20 (25.3%), respectively (**Table 3**). For both surveillance delay durations, the differences between polyps sized 1–3 mm, 1–5 mm, and 1–10 mm, were statistically significant (**Supplementary Table 7**).

In the patients for whom the optical diagnosis of 1–3mm polyps resulted in either 2- or 7-year delay compared to the surveillance intervals calculated based on the pathology results (n=3), 33.3% (1/3), and 66.7% (2/3) of delays were due to misdiagnosing an adenoma and a villous component, respectively.

In the patients for whom the optical diagnosis of 1–5mm polyps resulted in either 2- or 7-year delay compared to the surveillance intervals calculated based on the pathology results (n=12), 16.7% (2/12), and 83.3% (10/12) of delays were due to misdiagnosing an adenoma, and misdiagnosing a villous component, respectively.

In the patients for whom the optical diagnosis of 1–10 mm polyps resulted in either 2- or 7-year delay compared to the surveillance intervals calculated based on the pathology results (n=20), 10% (2/20), and 90% (18/20) of delays were due to misdiagnosing an adenoma, and misdiagnosing a villous component, respectively.

3.4 Surveillance Interval Agreements

Surveillance interval agreements are presented in **Figure 1**. In the whole cohort of patients (n=3374), the agreement between surveillance intervals based on the high-confidence optical diagnosis of polyps 1–3 mm and pathology-based recommendations was 97.2% (95% CI, 0.97–0.98). Moreover, the agreements between high-confidence optical diagnosis with polyp size cut-offs of 1–5 mm and 1–10 mm and pathology-based recommendations were 95.5% (95% CI, 0.95–0.96), and 94.2% (95% CI, 0.93–0.95), respectively (all *P<0.0001*) (**Figure 1**).

In the cohort of patients in which patients with normal colonoscopy, polyps >10 mm, and poor bowel preparation were excluded, the agreements between surveillance intervals based on the

high-confidence optical diagnosis of polyps 1–3 mm, 1–5 mm, and 1–10 mm and pathology-based recommendations were 96.2% (95% CI, 0.95–0.97), 93.6% (95% CI, 0.92–0.95), and 92.1% (95% CI, 0.91–0.93), respectively. The agreements between polyps 1–3 mm and 1–5 mm, between 1–3 mm and 1–10 mm, and between 1–5 mm and 1–10 mm were different (*P <0.0001*).

The details of surveillance interval agreements are presented in **Supplementary Tables 3 and 4**.

3.5 NPV for Neoplastic Rectosigmoid Polyps

Overall, 16.4%, 73.3%, and 8.2% of polyps 1–10 mm in size were optically predicted as hyperplastic (NICE 1), adenoma (NICE 2), and SSLs, respectively **(Supplementary Table 5)**.

The NPV of optical diagnosis for diagnosing rectosigmoid neoplastic polyps did not reach the recommended PIVI benchmark of ≥90% in any of the polyp size groups (1–3 mm: 81.4% [95% CI, 78.0–84.4]; 1–5 mm: 80.9% [95% CI, 78.0–83.6]; 1–10 mm: 80.6% [95% CI, 77.7–83.3]). Moreover, the accuracy of optical diagnosis for distinguishing neoplastic from hyperplastic polyps (regardless of polyp location) was only moderate for all three polyp size groups (1–3 mm: 78.3% [95% CI, 76.7–79.9]; 1–5 mm: 80.3% [95% CI, 79.2–81.4]; 1–10 mm: 81.0% [95% CI, 80.0–82.0]). The diagnostic characteristics of optical diagnosis can be found in **Table 4**.

3.6 Reduction in Histopathology Examinations and Allocation of Immediate Surveillance Intervals

Use of optical diagnosis would have resulted in a 33.5% (95% CI, 0.32–0.35), 62.3% (95% CI, 0.61–0.63), and 78.2% (95% CI, 0.77–0.80) reduction in histopathology examinations for polyps of 1–3 mm, 1–5 mm, and 1–10 mm, respectively (**Figure 2**). Furthermore, optical diagnosis could have allowed 41.0% (95% CI, 0.39–0.43), 58.2% (95% CI, 0.56–0.60), and 73.3% (95% CI, 0.72–0.75) of patients, respectively, to be given immediate, same-day surveillance interval recommendations. These proportions were greater than the corresponding proportions if the recommendations were followed based on pathology outcomes (*P <0.0001* for all, **Supplementary Table 7**).

4. Discussion

In this study that included 3374 patients with 7655 polyps undergoing optical diagnosis, we found that when limiting optical diagnosis to 1–3 mm polyps, the proportion of assigning delayed follow-up for patients having a polyp with advanced pathology was exceedingly low. Only a few polyps with serrated or villous pathology were found in the 1–3 mm group (n=73, 2.2%). If the optical diagnosis is limited to 1–3mm polyps, the proportion of delayed surveillance intervals for patients with advanced neoplastic polyps is lower compared to using optical diagnosis for polyps up to 5 mm or up to 10 mm. Using optical diagnosis for 1–3mm polyps exclusively resulted in only 0.5% of advanced neoplastic polyps and only 3 (3.8%) patients with a 7-year delay in the next surveillance colonoscopy. In contrast, when 4–10 mm polyps were included in the optical evaluation, 1.2% of polyps had advanced pathology, and 3 (3.8%) and 17 (21.5) patients had a 2-year and 7-year delay in their next surveillance colonoscopy, respectively. As the proportion of advanced pathology increases with polyp size ($p < 0.0001$), so does the rate of inappropriately delayed surveillance intervals.

Notably, we considered adenomas with a villous component as adenomas with advanced pathology. However, some studies found no association between villous adenomas and an increased risk of neoplasia.[23,24] The latest European Society of Gastrointestinal Endoscopy (ESGE) guideline[7] does not consider polyps with a villous component as "advanced" polyps. However, the 2020 USMSTF guidelines on which we based our study still consider these polyps as advanced. When villous polyps are excluded from advanced pathology criteria, the surveillance delays for 11 patients with advanced pathology were 9.1%, 18.2%, and 18.2% for 3, 5, and 10 mm cut-offs, respectively.

Discarding colorectal adenocarcinomas needs to be avoided when using optical diagnosis. It is often recommended to use NICE 3 classification for flat-depressed or ulcerated morphology (Paris IIc and III) to potentially identify adenocarcinomas among small polyps. A recent paper evaluating optical diagnosis for up to 10 mm polyps found that it would have resulted in discarding 5 T1 cancers without histopathology evaluation and taking appropriate management. In this study, the prevalence of T1 cancers among polyps 1–10 mm was 0.33%.[11] All cancers had Ip or Is morphology and were often judged through optical diagnosis as NICE 2 adenomas.[11] Thus, in the study above, as in our cohort with no found cancer, no correlation between NICE 3 and Paris IIc/III morphology was found to detect adenocarcinomas. In our cohort, out of 5346 polyps predicted

to be adenomas in the 1–10 mm polyps, 763 (14.3%) were evaluated to be hyperplastic or SSL during histopathology examination. We did not encounter any adenocarcinoma among 1–10 mm polyps. Thus, the best approach seems to be using a smaller cut-off to limit the risk of mismanaging advanced colorectal neoplasia within the "resect and discard" strategy.

Starting optical diagnosis at the low threshold of 1–3 mm might be feasible to ensure a cost-effective and safe approach to implementing the "resect and discard" strategy in routine clinical practice. Although the highest reduction in pathology examinations is naturally found when expanding optical diagnosis to 1–10 mm polyps (78.2%), limiting optical diagnosis to 1–3 mm polyps significantly reduces the need for pathology examinations (33.5%), concurring increasing the safety profile. Furthermore, a significant proportion of patients could have received an immediate surveillance recommendation, even when limiting optical diagnosis to 1–3 mm polyps (73.3% in the 1–10 mm group versus 41.0% in the 1–3 mm group).

The results of our study support the use of optical diagnosis for 1–3 mm polyps considering the recent evidence indicating the unreliability of histopathology assessment for this polyp size group. A recent study comparing optical diagnosis of 1–3 mm polyps with histopathology outcomes found that about 15% of polyps were reported as normal mucosa by pathology experts and adenoma by optical diagnosis.[25] Another study reported a similar discrepancy, with 28.9% of 1–3 mm polyps having mismatched optical and pathological diagnoses.[12] These findings suggest that high-confidence optical diagnosis is a safe method for accurate adenoma identification for 1–3 mm polyps, given the potential for pathology evaluations to report adenomatous polyps as normal mucosa. Furthermore, multiple recent studies have identified interrater variability between pathologists, or that expert high-confidence diagnoses of 1–3 mm polyps matched interpretation assisted by artificial intelligence (AI) but not the pathology results. Polyps previously diagnosed as hyperplastic might be reclassified as adenoma or SSAs after slide reassessment by another pathologist.[11,26-29]

The appropriate size cut-off for optical diagnosis is also relevant for future developments in AI-assisted optical diagnosis. AI-assisted optical diagnosis has improved detection with promising accuracy.[30,31] Despite recent research efforts in improving the diagnostic precision of AI models, similar to regular optical diagnosis, it cannot distinguish between different adenoma entities such as high-grade versus low-grade dysplasia, or reliably identify serrated or villous pathology.

Limiting optical diagnosis to 1–3 mm polyps will help decrease the risk of inappropriate management of advanced adenomas, regardless of the optical diagnosis modality used.

Some strengths and limitations of this study should be mentioned. To our knowledge, this is the first study to evaluate polyp size cut-offs for implementing optical diagnosis. We included the data from 2 academic centers with various endoscopists' optical diagnosis experiences, reflecting the real-world practice. Thus, it is possible to cautiously generalize the results to community practices. Study limitations include the post-hoc nature of the analysis, and the fact that polyp size was based on endoscopists' measurements. Endoscopists tend to overestimate polyp size compared with size measured during the pathological examination.[32,33] However, the method reflects the general clinical practice and remains a limitation until better techniques are widely available to improve real-time polyp measurement during colonoscopy. Additionally, the NICE classification system does not accurately distinguish SSLs from hyperplastic polyps resulting in misclassification of some polyps. Other optical diagnosis classification systems were not used because of the multiplicity of centers. The NICE classification has not been validated for blue light imaging; however, there was no decrease in diagnostic performance when compared with other optical imaging techniques.[34] One major limitation is the biased calculation of surveillance intervals due to the lack of data on the family history of CRC for patients from VA Medical Center. Consistent with other studies[11,35], our study did not reach the recommended NPV ≥90% PIVI benchmark to support using the "diagnose and leave" strategy for rectosigmoid polyps ≤10 mm. In a sub-analysis of per-endoscopist NPVs, only six expert endoscopists reached the recommended PIVI benchmark for implementing this strategy in each size group (**Supplementary Table 6**).

5. Conclusion

In conclusion, this study showed that limiting optical diagnosis to polyps 1–3 mm resulted in an excellent safety profile with a very low risk for inappropriate management of advanced adenomas, which makes routine clinical implementation of the "resect and discard" strategy feasible. Implementing a 3 mm cut-off could be a starting point for endoscopists to feel comfortable with the "resect and discard" strategy, with the potential of implementing a 5 mm

cut-off, once optical diagnosis becomes more popular, and endoscopists become more comfortable with its use.

6. References

1. Gupta N, Bansal A, Rao D, et al. Prevalence of advanced histological features in diminutive and small colon polyps. *Gastrointest Endosc* 2012; **75**(5): 1022-30.
2. Lieberman D, Moravec M, Holub J, Michaels L, Eisen G. Polyp size and advanced histology in patients undergoing colonoscopy screening: implications for CT colonography. *Gastroenterology* 2008; **135**(4): 1100-5.
3. 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**(8): 683-91.
4. Fan C, Younis A, Bookhout CE, Crockett SD. Management of Serrated Polyps of the Colon. *Curr Treat Options Gastroenterol* 2018; **16**(1): 182-202.
5. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2020; **158**(4): 1131-53 e5.
6. Chandran S, Parker F, Lontos S, Vaughan R, Efthymiou M. Can we ease the financial burden of colonoscopy? Using real-time endoscopic assessment of polyp histology to predict surveillance intervals. *Intern Med J* 2015; **45**(12): 1293-9.
7. Hassan C, Antonelli G, Dumonceau J-M, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2020. *Endoscopy* 2020; **52**(08): 687-700.
8. Rutter MD, East J, Rees CJ, et al. British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. *Gut* 2020; **69**(2): 201-23.
9. 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**(3): 419-22.
10. Bisschops R, East JE, Hassan C, et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2019. *Endoscopy* 2019; **51**(12): 1155-79.
11. Vleugels JLA, Hazewinkel Y, Dijkgraaf MGW, et al. Optical diagnosis expanded to small polyps: post-hoc analysis of diagnostic performance in a prospective multicenter study. *Endoscopy* 2019; **51**(3): 244-52.
12. Shahidi N, Rex DK, Kaltenbach T, Rastogi A, Ghalehjegh SH, Byrne MFJG. Use of Endoscopic Impression, Artificial Intelligence, and Pathologist Interpretation to Resolve Discrepancies Between Endoscopy and Pathology Analyses of Diminutive Colorectal Polyps. *Gastroenterology* 2020; **158**(3): 783-5. e1.
13. Alaoui A, Oumedjbeur K, Djinbachian R, et al. A79 CLINICAL VALIDATION OF THE SIMPLE CLASSIFICATION FOR OPTICAL DIAGNOSIS OF DIMINUTIVE AND SMALL COLORECTAL POLYPS. *Journal of the Canadian Association of Gastroenterology* 2020; **3**(Supplement_1): 93-4.
14. Djinbachian R, Pohl H, Marques P, et al. Sa2010 OPTICAL DIAGNOSIS OF SMALL COLORECTAL POLYPS USING OPTIVISTA AND ISCAN IMAGE ENHANCED ENDOSCOPY: A RANDOMIZED CONTROLLED TRIAL. *Gastrointestinal Endoscopy* 2020; **91**(6): AB240.
15. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ* 2015; **351**: h5527.

16. Von Renteln D, Leduc R, Bouchard S, et al. A78 Comparison of the Nice, Sano, and Wasp Classifications for Optical Diagnosis of Small Colorectal Polyps. *Journal of the Canadian Association of Gastroenterology* 2020; **3**(Supplement_1): 92-3.
17. Rex DK. Narrow-band imaging without optical magnification for histologic analysis of colorectal polyps. *Gastroenterology* 2009; **136**(4): 1174-81.
18. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**(6 Suppl): S3-43.
19. Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. *Am J Gastroenterol* 2012; **107**(9): 1315-29; quiz 4, 30.
20. Jass JR, Sobin LH, Morson BC. Histological typing of intestinal tumours. 2nd ed. Berlin ; New York: Springer-Verlag; 1989.
21. Fleiss JL, Levin B, Paik MC. Statistical methods for rates and proportions: john wiley & sons; 2013.
22. Landis JR, Koch GGJb. The measurement of observer agreement for categorical data. 1977: 159-74.
23. Bonithon-Kopp C, Piard F, Fenger C, et al. Colorectal adenoma characteristics as predictors of recurrence. *Dis Colon Rectum* 2004; **47**(3): 323-33.
24. Saini SD, Kim HM, Schoenfeld P. Incidence of advanced adenomas at surveillance colonoscopy in patients with a personal history of colon adenomas: a meta-analysis and systematic review. *Gastrointest Endosc* 2006; **64**(4): 614-26.
25. Ponugoti P, Rastogi A, Kaltenbach T, et al. Disagreement between high confidence endoscopic adenoma prediction and histopathological diagnosis in colonic lesions </= 3 mm in size. *Endoscopy* 2019; **51**(3): 221-6.
26. Schachschal G, Sehner S, Choschzick M, et al. Impact of reassessment of colonic hyperplastic polyps by expert GI pathologists. *Int J Colorectal Dis* 2016; **31**(3): 675-83.
27. Singh H, Bay D, Ip S, et al. Pathological reassessment of hyperplastic colon polyps in a city-wide pathology practice: implications for polyp surveillance recommendations. *Gastrointest Endosc* 2012; **76**(5): 1003-8.
28. Anderson JC, Lisovsky M, Greene MA, Hagen C, Srivastava A. Factors Associated With Classification of Hyperplastic Polyps as Sessile Serrated Adenomas/Polyps on Morphologic Review. *J Clin Gastroenterol* 2018; **52**(6): 524-9.
29. Baldin RKS, Anselmi Júnior RA, Azevedo M, et al. Interobserver variability in histological diagnosis of serrated colorectal polyps. *Journal of Coloproctology (Rio de Janeiro)* 2015; **35**: 193-7.
30. 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**(1): 94-100.
31. van der Sommen F, de Groof J, Struyvenberg M, et al. Machine learning in GI endoscopy: practical guidance in how to interpret a novel field. *Gut* 2020; **69**(11): 2035-45.
32. Anderson BW, Smyrk TC, Anderson KS, et al. Endoscopic overestimation of colorectal polyp size. *Gastrointest Endosc* 2016; **83**(1): 201-8.
33. Atalaia-Martins C, Marcos P, Leal C, et al. Variation between Pathological Measurement and Endoscopically Estimated Size of Colonic Polyps. *GE Port J Gastroenterol* 2019; **26**(3): 163-8.
34. Yoshida N, Hisabe T, Hirose R, et al. Improvement in the visibility of colorectal polyps by using blue laser imaging (with video). *Gastrointestinal Endoscopy* 2015; **82**(3): 542-9.
35. Sola-Vera J, Cuesta R, Uceda F, et al. Accuracy for optical diagnosis of colorectal polyps in clinical practice. *Rev Esp Enferm Dig* 2015; **107**(5): 255-61.

Table 1 Demographic and Clinical Characteristics of Patients.

Variables	**Frequency, n (%)**
Total number of patients	**3374 (100)**
Age, median (range), years	66.0 (45-80)
Sex (male)	2537 (75.2)
ASA class	
1	792 (23.5)
2	1871 (55.5)
3	711 (21.1)
Antithrombotic medication use (Yes)[a]	909 (26.9)
Family history of CRC in first-degree relatives (Yes)[b]	397 (11.8)
Colonoscopy characteristics [c]	
Colonoscopy indications	
Screening	998 (29.6)
FIT positive	144 (4.3)
Adenoma surveillance	1288 (38.2)
CRC surveillance	76 (2.3)
Anemia/bleeding	384 (11.4)
Diarrhea	86 (2.5)
Other[d]	396 (11.7)
Cecal intubation during colonoscopy (Yes)[e]	3260 (96.6)
Boston Bowel Preparation Scale ≥6[f]	3104 (92.0)
Number of patients with polyps	
No polyp	822 (24.4)
Polyp 1–3 mm	1684 (49.9)
Polyp 1–5 mm	2283 (67.7)
Polyp 1–10 mm	2477 (73.4)

ASA, American Society of Anesthesiologists; CRC, colorectal cancer; FIT, fecal immunochemical test. [a]Missing = 9 (0.3%). [b]Missing = 1936 (57.4%), information on the family history of CRC was only available for patients from CHUM center. [c]Missing = 2 (0.06%). [d]Other indications included surveillance due to family history of CRC, pre- and post-graft or organ donation, change in bowel habits such as constipation, post-polypectomy surveillance, screening for inflammatory diseases, ruling out diverticulitis, abdominal pain, celiac disease follow-up. [e]Missing = 2 (0.06%). [f]Missing = 11 (0.3%).

Table 2 Characteristics of the Detected Polyps Stratified by Size.

Clinicopathological characteristics of polyps	**Polyp size cut-off**		
	1–3 mm	**1–5 mm**	**1–10 mm**
Number of polyps, n/N (%)	**3278/7655 (42.8)**	**5906/7655 (77.1)**	**7291/7655 (95.2)**
Anatomical location, n (%)			
From cecum to descending colon	2432 (74.2)	4448 (75.3)[a]	5472 (75.1)[b]
Rectosigmoid colon	846 (25.8)	1458 (24.7)	1819 (24.9)
Polyp size, mean (standard deviation), mm	2.4 (0.6)	3.4 (1.2)	4.2 (2.0)
Histopathology results, n (%)			
Hyperplastic polyps	738 (22.5)	1259 (21.3)	1453 (19.9)
Tubular adenoma	1997 (60.9)	3718 (63.0)	4648 (63.7)
Tubulovillous adenoma	11 (0.3)	24 (0.4)	64 (0.9)
Villous adenoma	2 (0.1)	5 (0.1)	8 (0.1)
Traditional serrated adenoma	3 (0.1)	4 (0.1)	10 (0.1)
Sessile serrated adenoma/polyp	70 (2.1)	200 (3.4)	343 (4.7)
High-grade dysplasia	-	1 (0.02)	2 (0.03)
Other benign lesions	457 (13.9)	695 (11.8)	763 (10.5)
Polyps with advanced pathology[c], n (%)	16 (0.5)	34 (0.6)	84 (1.2)
Serrated lesions[d], n (%)	73 (2.2)	204 (3.5)	353 (4.8)

[a]Missing = 3 (0.1%). [b]Missing = 5 (0.1%). [c]Including tubulovillous adenoma and villous adenoma, traditional serrated adenoma, polyp with high-grade dysplasia and cancer. [d]Including sessile serrated adenoma, traditional serrated adenoma.

Table 3 Number of Patients with Surveillance Delays for 79 Patients with Advanced Pathology.

Patients with advanced polyps up to 3, 5, and 10 mm in size (n)	**No delay, n (%)[a]**	**2-year delay, n (%)[a]**	**7-year delay, n (%)[a]**	**Total, n (%), (95% confidence interval)**
1–3 mm[b] (14)	11 (13.9)	0 (0)	3 (3.8)	3 (3.8), (0.008-0.1)
1–5 mm[c] (32)	20 (25.3)	2 (2.5)	10 (12.6)	12 (15.2), (0.1-0.2)
1–10 mm[d] (79)	59 (74.6)	3 (3.8)	17 (21.5)	20 (25.3), (0.2-0.4)

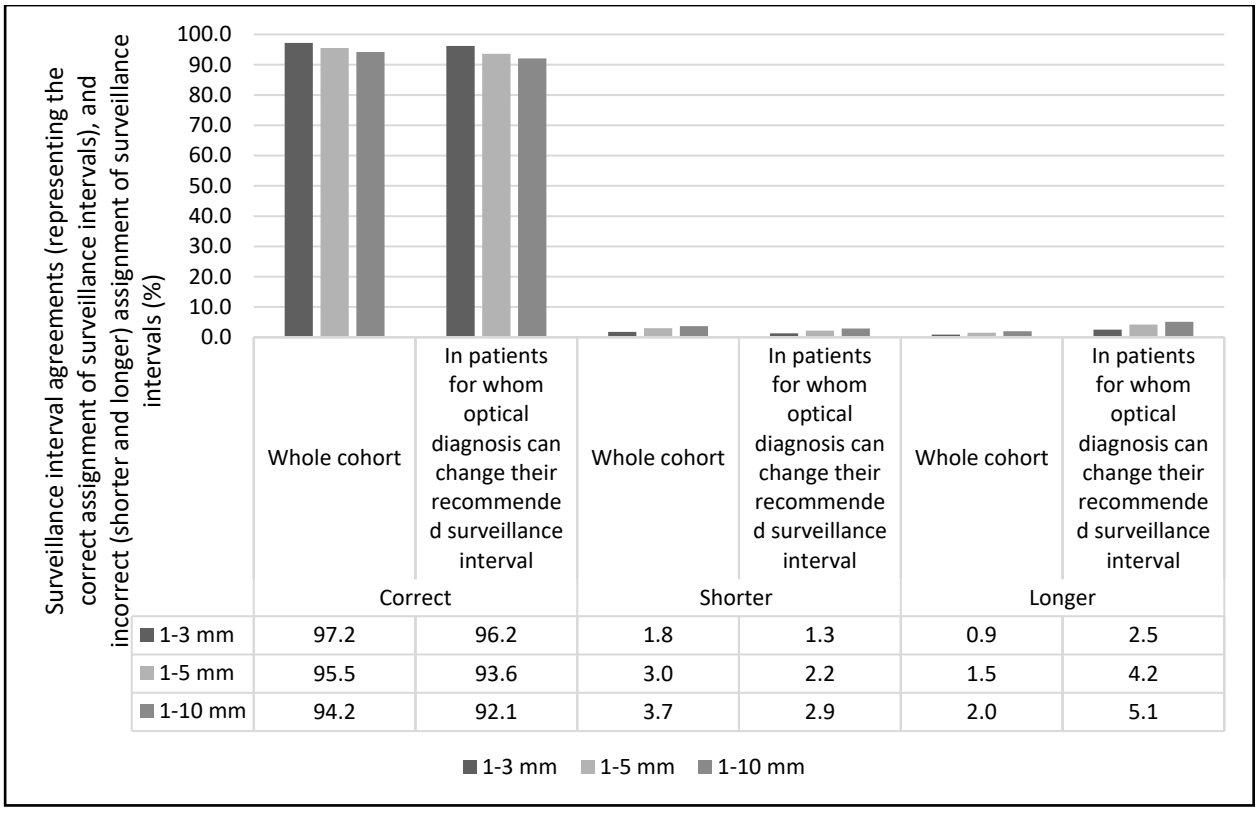
[a]Compared with surveillance intervals based on pathology results; [b]Missing=2 (2.5); [c]Missing=4(5.1); [d]Missing=8(10.1)

Table 4 Diagnostic Properties of Optical Diagnosis for Differentiating Hyperplastic from Adenomatous Polyps in Patients with at Least One Polyp 1–3, 1–5, 1–10 mm in Size, respectively.

Polyp size cut-off	Diagnostic properties (Adenoma vs hyperplastic)			
	In rectosigmoid polyps		In all polyps	
	%	95% CI	%	95% CI
1–3 mm				
Sensitivity	73.8	68.0–79.0	88.0	86.5–89.4
Specificity	66.9	61.4–70.3	52.3	48.6–55.9
PPV	55.4	51.8–59.0	83.3	82.2–84.3
NPV	81.4	78.0–84.4	61.7	58.4–64.9
Accuracy	68.8	65.2–72.2	78.3	76.7–79.9
1–5 mm				
Sensitivity	78.9	75.1–82.4	91.4	90.5–92.3
Specificity	59.6	56.0–63.2	47.4	44.6–50.2
PPV	56.5	54.1–58.9	83.8	83.0–84.5
NPV	80.9	78.0–83.6	65.0	62.2–67.7
Accuracy	67.3	64.6–69.9	80.3	79.2–81.4
1–10 mm				
Sensitivity	83.8	80.8–86.4	92.6	91.8–93.4
Specificity	54.9	51.5–58.3	43.3	40.7–45.9
PPV	60.1	58.2–62.0	84.1	83.5–84.7
NPV	80.6	77.7–83.3	64.4	61.7–67.1
Accuracy	67.8	65.5–70.1	81.0	80.0–82.0

NOTE: Optical diagnosis using the NICE classification system and image-enhanced endoscopy. Sessile serrated polyps/adenomas were not considered in the analysis.

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.



	Correct		Shorter		Longer	
	Whole cohort	In patients for whom optical diagnosis can change their recommended surveillance interval	Whole cohort	In patients for whom optical diagnosis can change their recommended surveillance interval	Whole cohort	In patients for whom optical diagnosis can change their recommended surveillance interval
1-3 mm	97.2	96.2	1.8	1.3	0.9	2.5
1-5 mm	95.5	93.6	3.0	2.2	1.5	4.2
1-10 mm	94.2	92.1	3.7	2.9	2.0	5.1

Figure 1 The percentage of surveillance interval agreement (correct assignment of surveillance intervals) between histopathology and optical diagnosis in all patients with valid determination of surveillance intervals, and in patients for whom optical diagnosis could have affected their next recommended surveillance intervals, using the NICE classification system and different cut-off points for size.

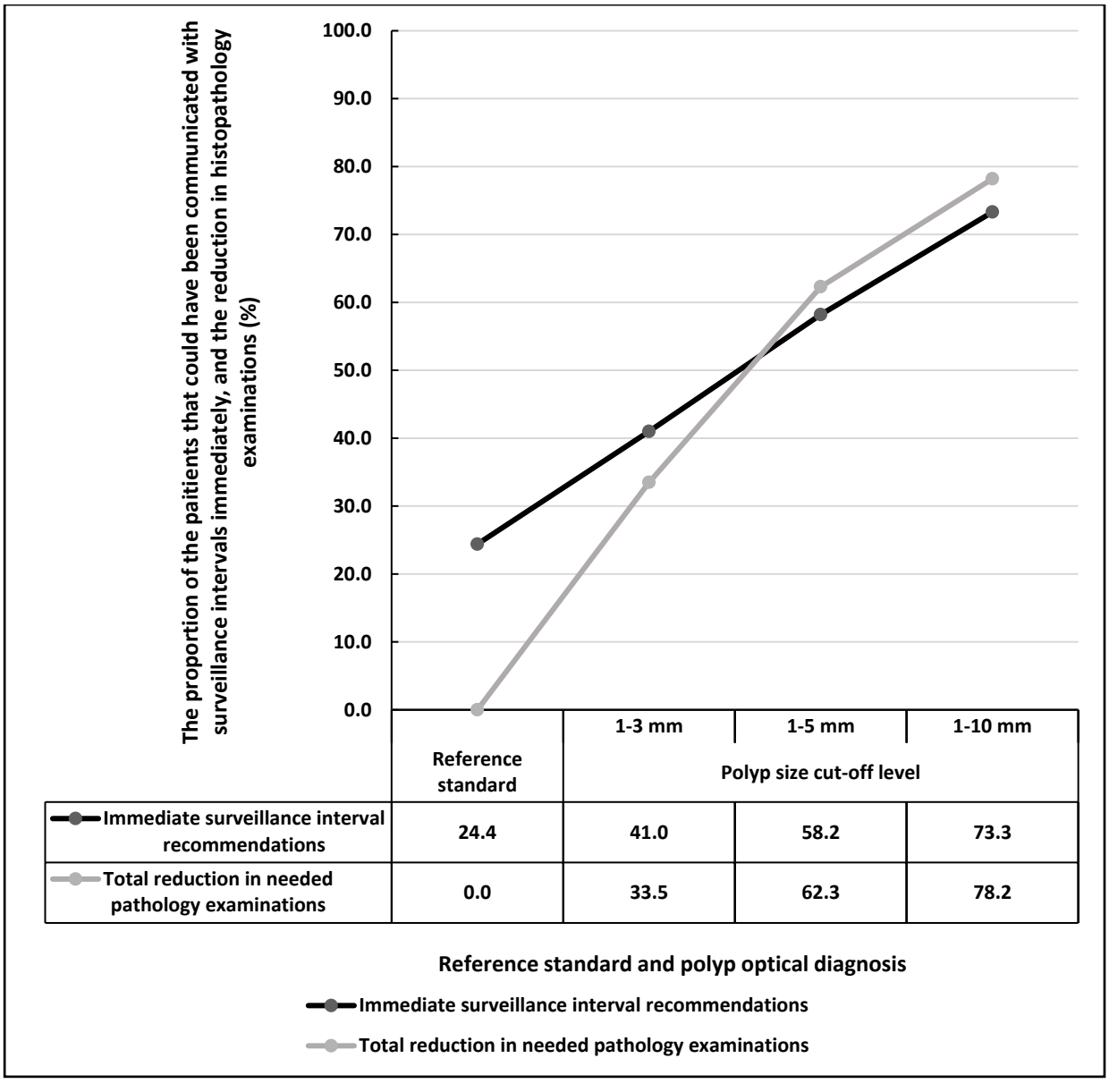


Figure 2 The total reduction in histopathology examinations and the proportion of patients who could have received immediate surveillance interval recommendations. The total reduction in histopathology examination was calculated for all polyps with or without advanced pathology.

Supplementary Table 1 Patients' characteristics in the CHUM and the Dartmouth centers.

Variables	**Frequency, n (%)**	**Study 1, CHUM center, n (%)**	**Study 2, CHUM center, n (%)**	**Study 3, Dartmouth center, n (%)**	**P-value of the difference between the CHUM and the Dartmouth centers**
Total number of patients	**3374 (100)**	**1058**	**383**	**1933**	
Age, median (range), years	66.0 (45-80)	63.0 (45-80)	62.4 (45.1-80)	68.0 (45-80)	<0.001
Sex (male)	2537 (75.2)	550 (52.0)	170 (44.4)	1817 (94.0)	<0.001
ASA class					<0.001
1	792 (23.5)	475 (44.9)	225 (58.7)	92 (4.8)	
2	1871 (55.5)	504 (47.6)	148 (38.6)	1219 (63.1)	
3	711 (21.1)	79 (7.5)	10 (2.6)	622 (32.2)	
Antithrombotic medication use (Yes)	909 (26.9)	226 (21.4)	60 (15.7)	623 (32.2)	0.012
Family history of CRC in first-degree relatives (Yes)	397 (11.8)	302 (28.6)	95 (24.9)	NA	0.243 between 2 CHUM studies
Colonoscopy characteristics					
Colonoscopy indications					
Screening	998 (29.6)	331 (31.3)	113 (29.5)	554 (28.7)	0.1863 for screening colonoscopies
Adenoma surveillance	1288 (38.2)	215 (20.3)	81 (21.1)	992 (51.3)	<0.001 for surveillance colonoscopies
CRC surveillance	76 (2.3)	37 (3.5)	6 (1.6)	33 (1.7)	
Anemia/bleeding	384 (11.4)	194 (18.4)	60 (15.7)	130 (6.7)	<0.001 for diagnostic colonoscopies
FIT positive	144 (4.3)	31 (2.9)	16 (4.2)	97 (5.0)	
Diarrhea	86 (2.5)	41 (3.9)	10 (2.6)	35 (1.8)	
Other[d]	396 (11.7)	208 (19.7)	97 (25.3)	91 (4.7)	
Cecal intubation during colonoscopy (Yes)[e]	3260 (96.6)	996 (94.3)	361 (94.3)	1903 (98.4)	<0.001
Boston Bowel Preparation Scale ≥6	3104 (92.0)	934 (88.3)	337 (88.0)	1833 (94.8)	<0.001

Supplementary Table 2 The significance of the difference between different outcomes and their corresponding 95% confidence intervals.

Method	Pairwise contrasts	Group 1-2		Group 1-3		Group 2-3	
		Adjusted significance	95% confidence interval	Adjusted significance	95% confidence interval	Adjusted significance	95% confidence interval
Without considering the random effect of centers[1]	Polyps with advanced pathology	0.58	-0.003 to 0.002	<0.0001	-0.01 to -0.003	<0.0001	-0.009 to -0.003
	Delayed surveillance intervals	0.001	-0.19 to -0.05	<0.0001	-0.34 to -0.14	0.003	-0.20 to -0.04
	Immediate recommendations	<0.0001	0.20 to 0.23	<0.0001	0.39 to 0.42	<0.0001	0.17-0.20
	Reduction in needed pathology examination	<0.0001	0.02 to 0.04	<0.0001	0.03 to 0.05	<0.0001	0.01 to 0.02
Considering the random effect of centers[2]	Polyps with advanced pathology	-	-	-	-	-	-
	Delayed surveillance intervals	0.012	-0.22 to -0.03	<0.0001	-0.36 to -0.13	0.08	-0.26 to 0.01
	Immediate recommendations	<0.0001	0.27 to 0.32	<0.0001	0.56 to 0.61	<0.0001	0.27 to 0.31
	Reduction in needed pathology examination	0.03	1.289E-9 to 2.233E-8	0.001	8.804E-9 to 3.676E-8	0.01	2.662E-9 to 1.928E-8
Considering the mutually exclusive categories and random effect of centers[3]	Polyps with advanced pathology	0.33	-0.01 to 0.002	<0.0001	-0.04 to -0.02	<0.0001	-0.04 to -0.02
	Delayed surveillance intervals	-	-	-	-	-	-
	Immediate recommendations	-	-	-	-	-	-
	Reduction in needed pathology examination	<0.0001	0.03 to 0.08	<0.0001	0.07 to 0.11	<0.0001	0.02 to 0.06
Phi coefficient of correlation[4]	Polyps with advanced pathology	<0.0001	-	<0.0001	-	<0.0001	-
	Delayed surveillance intervals	<0.0001	-	<0.0001	-	<0.0001	-
	Immediate recommendations		-		-		-
	Reduction in needed pathology examination	<0.0001	-	<0.0001	-	<0.0001	-

1) Generalized linear models with logit link without considering the random effect of centers; 2) Generalized linear mixed models with a logit link to consider the random effect of centers to compare the size groups when each size group was considered as one repeated measure; 3) Generalized linear models with logit link between mutually

inclusive size groups (i.e., 1–3mm, 4-5 mm, 6-10 mm) only for comparisons of the advanced histology and the reduction in the pathology examinations; 4) the Phi coefficient of correlation.
Group 1: 1–3mm polyps; group2: 1–5mm polyps; group3: 1–10 mm polyps.

Supplementary Table 3 Clinicopathological characteristics of polyps with advanced histology, which were optically diagnosed during endoscopies.

Polyp size (millimetre = mm)			1–3mm				1–5mm				1–10 mm			
Anatomical location	Optical diagnosis confidence level	Histopathology results	Optical polyp classification based on NICE classification[a]			Total	Optical polyp classification based on NICE classification[a]			Total	Optical polyp classification based on NICE classification[a]			Total
			Hyperplastic polyp	Adenoma	Malignancy		Hyperplastic polyp	Adenoma	Malignancy		Hyperplastic polyp	Adenoma	Malignancy	
From cecum to descending colon	High	Villous/tubulovillous adenoma	1	4	0	5	1	12	1	14	2	45	1	48
		Traditional serrated adenoma	0	1	0	1	0	1	1	2	0	3	4	7
		High-grade dysplasia	0	0	0	0	0	1	0	1	0	2	0	2
	Low	Villous/tubulovillous adenoma	1	2	2	5	1	3	2	6	2	4	3	9
		Traditional serrated adenoma	0	1	0	1	0	1	0	1	0	1	0	1
Rectosigmoid colon[b]	High	Villous/tubulovillous adenoma	1	0	0	1	1	6	0	7	1	6	0	7
		Traditional serrated adenoma	0	0	0	0	0	0	0	0	0	1	0	1
Total						13				31				75

[a] NICE= Narrow-band Imaging International Colorectal Endoscopic; [b]No polyp were optically diagnoses with low confidence in rectosigmoid colon; [c]Missing = 66 (2.1%). Light gray color represents the underdiagnosis and dark gray color represents overdiagnosis by optical polyp diagnosis compared to histopathology results as the reference standard.

Supplementary Table 4 Measurement of surveillance interval agreement between optical diagnosis and histopathology outcomes in a whole cohort of patients.

Optical surveillance intervals		Considering optical prediction of histology for polyps of 1–3mm in size					Considering optical prediction of histology for polyps of 1–5mm in size					Considering optical prediction of histology for polyps of 1–10 mm in size				
Surveillance intervals based on histopathology outcomes (years)		**1**	**3**	**5**	**10**	**Total**	**1**	**3**	**5**	**10**	**Total**	**1**	**3**	**5**	**10**	**Total**
Surveillance intervals based on NICE classification system (years)	**1**	192	4	0	0	196	192	4	0	0	196	189	9	0	0	198
	3	1	536	11	1	549	1	513	21	4	539	1	491	34	5	531
	5	0	7	583	45	635	0	12	563	68	643	0	15	543	73	631
	10	0	3	20	1892	1915	0	10	28	1849	1887	0	18	32	1832	1882
Total		193	550	614	1938	3295	193	539	612	1921	3265	190	533	609	1910	3242

*The concordant values have been highlighted.

Supplementary Table 5 Measurement of surveillance interval agreement between optical diagnosis and histopathology outcomes in patients with only polyps ≤10 mm (without large polyps), without normal colonoscopy, without poor bowel preparation, and valid assignment of surveillance intervals by histopathology outcomes and optical diagnosis.

Optical surveillance intervals		Considering optical prediction of histology for polyps of 1–3mm in size				Considering optical prediction of histology for polyps of 1–5mm in size				Considering optical prediction of histology for polyps of 1–10 mm in size			
Surveillance intervals based on histopathology outcomes (years)		**3**	**5**	**10**	**Total**	**3**	**5**	**10**	**Total**	**3**	**5**	**10**	**Total**
Surveillance intervals based on NICE classification system (years)	**3**	277	11	1	289	258	21	4	283	239	32	5	276
	5	7	414	45	466	12	394	68	474	15	377	73	465
	10	3	20	1493	1516	10	28	1450	1488	18	32	1433	1483
Total		287	445	1539	2271	280	443	1522	2245	272	441	1511	2224

Supplementary Table 6 Prediction of the histology of polyps 1–10 mm by optical strategy NICE classification systems.

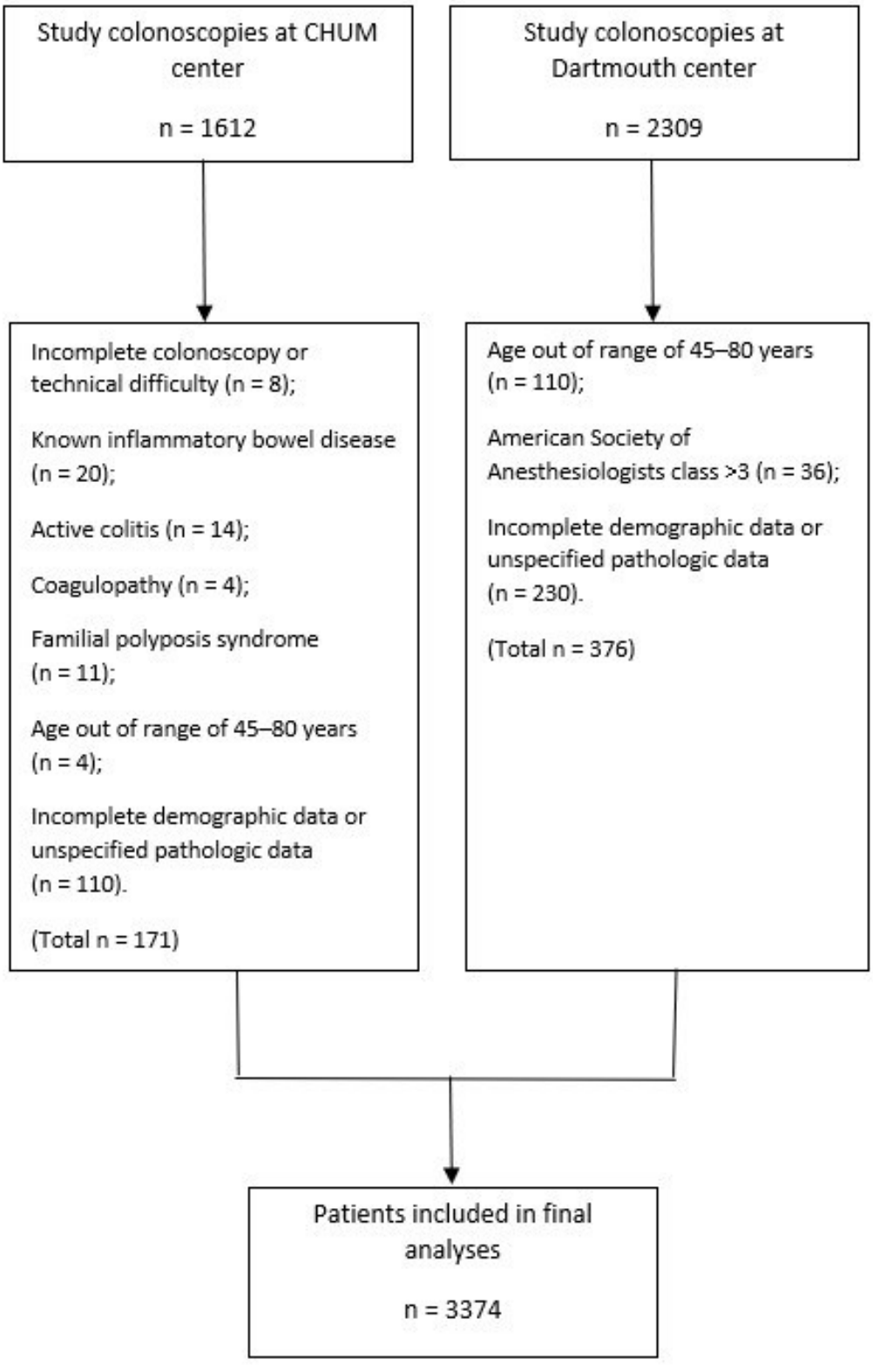
Optical polyp classification based on NICE classification system	Polyp size		
	1–3mm	**1-5mm**	**1–10 mm**
Confidence level (high)	2588 (79.0) [a]	4813 (81.5) [b]	6033 (82.7) [c]
Hyperplastic	779 (23.8)	1123 (19.0)	1199 (16.4)
Adenoma	2278 (69.5)	4262 (72.2)	5346 (73.3)
SSL	155 (4.7)	397 (6.7)	597 (8.2)
Missing	66 (2.1)	124 (2.1)	149 (2.0)

[a]Missing = 90 (2.7); [b]Missing = 170 (2.9); [c]Missing = 219 (3.0%); NICE: NBI International Colorectal Endoscopic; SSL: sessile serrated lesions.

Supplementary Table 7 Negative predictive value of "diagnose and leave" for differentiating hyperplastic from adenomatous polyps in patients with at least one polyp 1–3, 1–5, 1–10 mm in size, respectively, for individual expert endoscopists.

Negative predictive value in rectosigmoid polyps (adenoma vs. hyperplastic) (%, 95% confidence interval)			
Polyp size cut-off	**1–3 mm**	**1–5 mm**	**1–10 mm**
Endoscopist 1	63.6 (51.6-74.2)	68.3 (57.3-77.6)	62.5 (52.8-71.3)
Endoscopist 2	62.5 (34.1-84.3)	44.4 (22.3-68.9)	54.5 (32.3-75.1)
Endoscopist 3	35.3 (28. 7-42.5)	35.3 (27.7-43.7)	35.0 (26.2-44.9)
Endoscopist 4	43.7 (27.4-61.6)	38.9 (24.5-55.5)	38.9 (23.4-57.1)
Endoscopist 5	50.0 (7.7-92.3)	50.0 (7.7-92.3)	50.0 (7. 7-92.3)
Endoscopist 6	57.1 (33.0-78.3)	72.7 (50.8-87.3)	69.2 (47.2-85.0)
Endoscopist 7	42.9 (20.6-68.4)	42.9 (19.5-69.9)	42.9 (19.3-70.2)
Endoscopist 8	66.7 (32.3-89.3)	80.0 (35.2-96.7)	60.0 (35.7-80.2)
Endoscopist 9	25.0 (11.7-45.6)	44.4 (29.1-61.0)	44.4 (28.7-61.5)
Endoscopist 10	95.4 (75.2-99.3)	91.7 (78.3-97.1)	92.1 (79.1-97.3)
Endoscopist 11	87.2 (74.2-94.1)	92.1 (85.5-95.8)	92.4 (85.8-95.7)
Endoscopist 12	85.1 (73.1-92.3)	84.5 (75.0-90.9)	84.6 (75.5-90.8)
Endoscopist 13	87.9 (73.9-94.9)	88.1 (75.7-94.6)	88.1 (75.5-94.7)
Endoscopist 14	71.4 (40.8-90.1)	75.0 (44.5-91.8)	75.0 (43.9-92.0)
Endoscopist 15	83.3 (46.4-96.6)	85.7 (48.3-97.5)	85.7 (46.5-97.6)

Note: negative predictive values were calculated for endoscopists with sufficient polyps and were 100% for four endoscopists.



Supplementary Figure 1 Patients' selection flowchart.

Chapter 2 – Article 2

The Location-Based Resect and Discard Strategy for Diminutive Colorectal Polyps: A Prospective Clinical Study

Mahsa Taghiakbari,[1,2] Heiko Pohl,[3,4] Roupen Djinbachian,[2,5] Alan Barkun,[6] Paola Marques,[7] Mickael Bouin,[2,8] Eric Deslandres,[8] Benoit Panzini,[8] Simon Bouchard,[2,8] Audrey Weber,[2,8] Daniel von Renteln[2,8]

[1] University of Montreal, Montreal, Quebec, Canada; [2] University of Montreal Hospital Research Center (CRCHUM), Montreal, Quebec, Canada; [3] Department of Veterans Affairs Medical Center, White River Junction, Vermont, United States; [4] Dartmouth Geisel School of Medicine and The Dartmouth Institute, Hanover, New Hampshire, United States; [5] Division of Internal Medicine, University of Montreal Hospital Center (CHUM), Montreal, Quebec, Canada; [6] Division of Gastroenterology, McGill University Health Center, McGill University, Montreal, Quebec, Canada; [7] Faculty of Medicine, Bahia State University, Salvador, Bahia, Brazil; [8] Division of Gastroenterology, University of Montreal Hospital Center (CHUM), Montreal, Quebec, Canada

ABSTRACT

Background and study aim: Clinical implementation of the resect and discard strategy has been difficult because optical diagnosis is highly operator dependent. This prospective study aimed to evaluate a resect and discard strategy that is not operator dependent.

Patients and methods: The study evaluated a resect and discard strategy that uses anatomical polyp location to classify colon polyps into non-neoplastic or low-risk neoplastic. All rectosigmoid diminutive polyps were considered hyperplastic and all polyps located proximally to the sigmoid colon were considered neoplastic. Surveillance interval assignments based on these a priori assumptions were compared with those based on actual pathology results and optical diagnosis, respectively. The primary outcome was ≥90% agreement with pathology in surveillance interval assignment.

Results: Overall, 1117 patients undergoing complete colonoscopy were included and 482 (43.1%) had at least one diminutive polyp. Surveillance interval agreement between the location-based strategy and pathological findings using the 2020 US Multi-Society Task Force guideline was 97.0% (95% CI=0.96–0.98), surpassing the ≥90% benchmark. Optical diagnoses using NICE and Sano classifications reached 89.1% and 90.01% agreement, respectively ($p<0.0001$), and were inferior to the location-based strategy. The location-based resect and discard strategy allowed a 69.7% (95% CI=0.67-0.72) reduction in pathology examinations compared with 55.3% (95% CI=0.52-0.58) (NICE and Sano) and 41.9% (95% CI=0.39-0.45) (WASP) with optical diagnosis.

Conclusion: The location-based resect and discard strategy achieved very high surveillance interval agreement with pathology-based surveillance interval assignment, surpassing the ≥90% benchmark and outperforming optical diagnosis in surveillance interval agreement and the number of pathology examinations avoided.

Keywords: Colonoscopy; Colorectal Pathology; Colorectal Adenomas; Endoscopy; Surveillance.

1. Introduction

Optical polyp diagnosis (OD) based on image-enhanced endoscopy (IEE) allows for classification of diminutive polyps into neoplastic and non-neoplastic.[1] As the majority of colorectal polyps found during colonoscopies are diminutive (≤5 mm) and have a low risk for harbouring advanced histology,[2,3] replacing histopathology evaluation with OD has been deemed a cost-effective and safe alternative.[3-5] This potential for cost-savings has led such as the American Society for Gastrointestinal Endoscopy (ASGE), the British Society of Gastroenterology (BSG) and the European Society of Gastrointestinal Endoscopy (ESGE) to issue guidelines to support and guide the practical implementation of the 'resect and discard' strategy.[6-9] The ASGE Technology Committee, in its Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) statement, recommended the implementation of the resect and discard strategy if it reaches ≥90% agreement with histopathology in determining post-polypectomy surveillance intervals.[6] However, the ASGE position paper emphasises that OD should be performed by adequately trained, monitored and audited endoscopists to increase the accuracy of OD and the proportion of high-confidence predictions of histology.[6,10,11] The ESGE considers training in OD as an important prerequisite for the implementation of IEE and recommends the use of validated classification systems to support the use of OD with advanced endoscopic imaging along with sufficient photo documentation.[9,12]

Although the concept of resect and discard presents a great potential to improve colonoscopy practice, its widespread clinical implementation has not been achieved. A recent survey revealed that endoscopists have failed to adopt the use of the resect and discard strategy in clinical practice because of concerns about making the wrong diagnosis and a subsequent erroneous surveillance interval assignment, with its potential medicolegal repercussions.[13]

To circumvent the problems associated with OD, we developed a simplified and operator-independent resect and discard strategy. This location-based resect and discard (LBRD) strategy does not rely on OD and does not require any special operator skills to be acquired or audited. Our group has recently published a retrospective study evaluating this concept.[14] The aim of the current prospective study was to determine how the LBRD strategy will perform in a prospective cohort when tested against OD.

2. Patients, Material and Methods

2.1 Study Setting and Population

The study population consisted of 1187 patients who presented at Montréal University Hospital Center (CHUM) between May 2017 and December 2018 for elective colonoscopy. Supplementary Figure 1 shows the flowchart of the study participants selection. Patients aged between 45 and 80 years undergoing screening, surveillance or diagnostic colonoscopies were eligible to be included in the study. Patients with known inflammatory bowel disease, active colitis, coagulopathy, familial polyposis syndrome, poor general health (American Society of Anesthesiologists class >3), undergoing emergency colonoscopies (procedures in the emergency or intensive care unit or patients with active upper or lower gastrointestinal bleeding), missing or non-definitive information on demographic or colonoscopy characteristics, and age out of the pre-defined study range were excluded (n=70). Of the 1117 patients included in the study, 635 were found to have only larger polyps (>5 mm) or a normal colonoscopy. A total of 921 diminutive polyps were detected and 482 (43.1%) patients had at least one diminutive polyp. The study was approved by the Research Ethics Board of CHUM (CERCHUM; Research Ethics Committee number (CER)= 16.367) and registered under ClinicalTrials.gov (NCT04032912). Informed consent for study participation was obtained from each patient before colonoscopy.

2.2 Study Procedure

All patients were prepared for colonoscopy using a standard bowel cleansing preparation. A research assistant documented standard colonoscopy quality metrics such as cecal intubation, bowel preparation score (Boston Bowel Preparation Scale) and withdrawal time during the procedure. Size, location and morphological characteristics (using the Paris endoscopic classification[15]) of each detected polyp were documented. All detected polyps were removed and sent for histopathology evaluation as per institutional standard of care.

2.3 Histopathological Assessment

The histopathological assessment was performed by board-certified pathologists at CHUM, according to current practices and institutional standards for all polyps. Polyps were categorised

as neoplastic and non-neoplastic. Neoplastic polyps were defined as all adenomatous polyps including cancerous and all sessile serrated adenomas/polyps (SSA/Ps).[16] Advanced adenomas were defined as all diminutive polyps with a villous component, or exhibiting high-grade dysplasia in the absence of invasive colorectal cancer (CRC).[4]

2.4 Location-Based Resect and Discard Strategy

The LBRD strategy was applied in the following manner: all diminutive polyps anatomically located in the rectosigmoid colon were a priori considered as being non-neoplastic (hyperplastic polyps) while all diminutive polyps located in the proximal colon (from caecum to descending colon) were considered neoplastic (low-risk adenomatous polyps). This model thus uses the anatomical location of a diminutive polyp as the sole criterion for predicting histology (neoplastic vs non-neoplastic) and does not depend on OD criteria.

2.5 Optical Diagnosis and Classification Systems

Ten experienced endoscopists performed the colonoscopies. All endoscopists underwent formal training in narrow-band imaging (NBI) OD of colorectal polyps before including their first study patient. All detected diminutive polyps underwent IEE using i-Scan OE (Pentax Medical, Tokyo, Japan) and were classified according to their surface and vascular patterns using three different OD classification systems. The NBI magnification was available to be used at the endoscopists' discretion. During OD, each endoscopist made a real-time prediction of each polyp histology according to NBI International Colorectal Endoscopic (NICE),[17] Workgroup serrAted polypS and Polyposis (WASP)[18] and Sano[19-21] classification systems.[22] A research assistant documented polyp characteristics, pathology predictions, and endoscopists' level of confidence (low or high) for their histology prediction during the procedure. Patients with missing documentation on OD for diminutive polyps, or on histopathology reports (i.e., polyp resected but not retrieved [2.3%]) were excluded from analyses.

2.6 Surveillance Interval Assignment

Each patient was assigned a surveillance interval based on a) the LBRD strategy, and real-time OD using the b) NICE classification, c) Sano classification, and d) WASP classification. For calculation of surveillance intervals, all concomitant adenomas >5 mm, poor bowel preparation and positive family history of CRC were considered in the final decision for all used strategies.

After histopathological assessment of polyps, surveillance intervals were assigned based on histopathological outcomes in order to obtain a reference standard. Both the 2012 and 2020 US Multi-Society Task Force (USMSTF) guidelines were used for calculation of pathology-based surveillance intervals to address the impact of changes in the new guideline on actual practice.[4,23] Surveillance interval assignments according to the LBRD strategy and optical diagnoses were then compared with pathology-based assignments. If the guideline suggested a time period for surveillance interval, the longer end of the interval was used (e.g., 10 years for surveillance interval of 5–10 years) for comparison and determination of agreement between pathology and resect and discard/OD strategies.

2.7 Study Outcomes

The primary outcome of the study was the surveillance interval agreement of the LBRD strategy when compared with the pathology-based reference standard for the complete cohort of patients, and for a sub-cohort of patients with adequate bowel preparation.[6] The surveillance intervals for OD using i-Scan and different validated classification systems (NICE, Sano, WASP) were also compared with the pathology-based intervals.

Secondary outcomes were the diagnostic properties of the LBRD strategy and optical diagnoses, including accuracy, sensitivity, specificity, positive predictive value (PPV) and, particularly, negative predictive value (NPV), to determine whether the ASGE PIVI benchmark of ≥90% NPV to diagnose neoplastic diminutive rectosigmoid polyps can be reached.[6]

Additional secondary outcomes were the calculation of the proportion of patients who could have received an immediate notification of surveillance interval, and the proportion of histopathology examinations could have been avoided using the different strategies.

2.8 Sample Size Calculation

The sample size calculation for our primary outcome was based on the surveillance interval agreement of the LBRD strategy compared to the pathology-based surveillance interval recommendations. We assumed that the LBRD strategy can achieve a 92.5% agreement with pathology-based recommendations. For the lower margin of the 95% confidence interval (CI) to be above 90% (quality benchmark proposed by the ASGE), we will need to enrol at least 480 patients in whom at least one diminutive polyp is found. Considering a prevalence of 45% neoplastic and non-neoplastic diminutive polyps in our study cohort and a potential rate of about 5% pathology specimens that cannot be retrieved from the colon, we will need to screen at least a total of 1,091 patients.

2.9 Statistical Analyses

The study reports diagnostic accuracy following the STAndards for the Reporting of Diagnostic accuracy studies (STARD) guidelines.[24] Descriptive statistics are presented as numbers and frequencies for categorical variables, and mean ± standard deviation (SD) or median (range) for continuous variables with normal and non-normal distribution, respectively, as necessary.

The surveillance interval agreement between the location-based strategy, OD, and histopathology results are presented as proportions with 95% CIs. Agreements were compared among different strategies using McNemar's test with a two-tailed significance level of $p<0.05$. The proportions of correct and incorrect (shorter or longer) surveillance intervals compared with the reference standard are also presented.

The diagnostic properties of OD and the LBRD strategy were calculated, including sensitivity, specificity, PPV, NPV and accuracy. Based on the prior definition of the 2020 USMSTF guideline, we categorised diminutive polyps into hyperplastic and adenomas.

The proportion of patients who could have received immediate surveillance interval recommendations according to the different strategies were calculated as follows: a) reference value – the total number of patients without polyp identification during colonoscopy (normal colonoscopy) divided by the total number of patients; b) location-based strategy – the sum of the number of patients without any polyps plus the patients with only diminutive polyps divided by the total number of patients; c) OD using each classification – the sum of the number of all

patients without any polyps plus the patients with only diminutive polyps optically diagnosed with high confidence divided by the total number of patients. The proportion of pathology examinations needed was calculated as follows: a) reference value – the number of polyps sent for histopathology evaluation divided by the total number of polyps; b) LBRD strategy – the number of non-diminutive polyps divided by the total number of polyps; c) OD using each classification, the number of diminutive polyps optically diagnosed with low confidence divided by the total number of polyps. All measurements were presented with 95% CIs.

SPSS version 26.0 (IBM Corp., Armonk, New York, USA) and MedCalc version 19.4 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org) were used for analyses.

3. Results

3.1 Patient, Procedures and Polyp Characteristics

A total of 1117 patients (median age 63.3 (minimum-maximum values=45.0-80.9) years; 52.3% male) were prospectively enrolled into the study. Table 1 presents details on demographic and clinical characteristics of the study patients. The majority of colonoscopies were performed for an indication of screening (30.7%) and adenoma surveillance (20.4%).

The polyp and adenoma detection rates were 58.0% and 38.5%, respectively. Of the 921 diminutive polyps detected, 906 (98.4%) were removed and 885 (96.1%) were retrieved. A total of 393 (42.7%) polyps were located in the rectosigmoid. Advanced histopathology was detected in 14 (1.5%) diminutive polyps. All polyps with the report of 'intramucosal cancer' in the histopathology reports were considered high-grade dysplasia to avoid confusion with CRC invading the submucosal layer.[25] No high-grade dysplasia or cancer was detected among patients with at least one diminutive polyps.

3.2 Surveillance Interval Agreement

In the whole cohort of patients with valid surveillance interval calculations, the agreement between the location-based and pathology-based determination of surveillance interval was 97% (95% CI=0.96-0.98) when using 2020 USMSTF guidelines and 93.6% (95% CI = 0.92-0.95)

when using 2012 USMSTF guidelines (significant difference between agreements according to the 2020 and 2012 guidelines, McNemar's p<0.0001). Moreover, the surveillance interval agreement of the LBRD strategy and pathology using 2020 guideline in patients with adequate bowel preparation was 96.6% (95% CI=0.95-0.98). The detailed agreement values and their corresponding CIs are shown in Figure 1.

Overall, use of different classification systems for OD did not affect the surveillance interval agreement. The agreement between surveillance intervals determined by OD using the NICE classification and pathology using the 2020 and 2012 USMSTF guidelines were 89.1% (95% CI=0.87-0.91) and 90.1% (95% CI=0.88-0.92), respectively. Moreover, OD using the Sano classification reached the ASGE PIVI benchmark using either the 2012 or 2020 USMSTF guidelines. However, OD using the WASP classification did not reach the recommended benchmark using either USMSTF guideline (87.9% vs 86.8%). Moreover, none of the optical classification systems could reach the recommended benchmark of 90% with pathology-based surveillance interval assignment in the cohort of patients with adequate bowel preparation (NICE classification system: 88% (95% CI=0.86-0.90); Sano classification system: 87.8% (95% CI=0.85-0.90); WASP classification system: 85.4% (95% CI=0.83-0.88)).

Surveillance interval agreement between the LBRD strategy and pathology using the 2020 guideline was significantly greater than the agreement between pathology and OD using NICE, Sano and WASP classifications (McNemar's p<0.0001 for all comparisons).

3.3 Accuracy of Surveillance Interval Assignment

Figure 2 shows the proportion of patients with at least one diminutive polyp who were assigned correct surveillance intervals. Use of the LBRD strategy resulted in more correct surveillance intervals compared to implementation of OD using any of the classification systems. Using the location-based strategy according to the 2020 USMSTF guideline, only 16 patients were assigned a longer surveillance interval, which was significantly lower than the number of patients assigned a longer surveillance interval by OD using WASP (52 patients), Sano (51 patients) and NICE (54 patients) classifications (number of patients calculated out of the whole cohort of patients with available pathology and OD results). Individual surveillance interval assignments by each method are presented in Supplementary Table 1. The results of the surveillance interval agreements in a

sub-cohort of the patients with adequate bowel preparation and only diminutive polyp are presented in Supplementary Table 2.

3.4 Diagnostic Properties of The Location-Based Resect and Discard and Optical Strategies

Table 2 presents the accuracy of the pathology prediction when using the LBRD strategy and OD using i-Scan.

Overall, the LBRD strategy could not surpass the ASGE PIVI benchmark of NPV ≥90% in distinguishing hyperplastic from neoplastic rectosigmoid polyps when including either all diminutive polyps throughout the colon or only rectosigmoid diminutive polyps. Furthermore, regardless of the classification system used for predicting polyp histology, OD also did not reach the PIVI benchmark for distinguishing hyperplastic from neoplastic polyps.

3.5 Location-Based Resect and Discard Strategy and Optical Diagnosis Benefits

The LBRD strategy could provide significantly higher proportion of patients with an immediate surveillance interval recommendation (76.7% (95% CI=0.74-0.79)) compared with OD using NICE and Sano classifications (67.4% (95% CI=0.65-0.70) (McNemar's $p<0.0001$) (Figure 3).

The total reduction in histopathology examinations following the LBRD strategy was 69.7% (95% CI = 0.67–0.72), which was significantly higher than the reduction following OD using NICE and Sano classifications (both 55.3%; McNemar's $p<0.0001$). The reduction in histopathology examinations for OD using the WASP classification was lower than for NICE and Sano classification systems (McNemar's $p<0.0001$) (Figure 3).

In a subgroup analysis amongst patients with at least one diminutive polyp (n = 482), 208 (43.2%) patients would have received an incorrect diagnosis using the LBRD strategy (Table 3). However, only 25 (5.2%) patients would have received an incorrect post-polypectomy surveillance interval recommendation. Among the remaining 183 patients, the majority were given the correct

surveillance interval based on the presence of ≤2 adenomas or hyperplastic polyps ≤10 mm in size.

4. Discussion

In this prospective clinical study, the operator-independent LBRD strategy performed well and above the 90% PIVI quality benchmark required for its clinical implementation for recommending surveillance interval as a replacement for pathology-based recommendations. No cancers were missed in our cohort of patients with diminutive polyps. The risk for delayed surveillance intervals was low implying the safe clinical implementation of this approach. The significantly greater surveillance interval agreement of the LBRD strategy with pathology using the 2020 guideline compared with the 2012 guideline explains the improved results compared with our previously published retrospective study.[14] The LBRD strategy would allow a greater number of patients receiving surveillance interval recommendations on the same day as the colonoscopy procedure, and fewer polyps requiring histopathology evaluation compared with OD and standard colonoscopy practice.

The findings offer a scheme for facilitating and overcoming the challenges of broad implementation of a resect and discard strategy in routine clinical practice. The LBRD strategy uses the anatomical location as the only criterion to predict polyp histology, making the surveillance interval assignment independent of the endoscopist's skill. The approach also eliminates the need for any advanced imaging technologies, and consequently increases the usefulness of conventional colonoscopy particularly in community-based practice settings that have limited access to optical and state-of-the-art equipment, or related training opportunities.

Implementation of the location-based strategy would also eliminate the need for the endoscopist to assign a confidence level to their histology prediction when using OD.[26]

Our results are aligned with previous publications.[22,27,28] As shown in previous studies,[29] the accuracy of OD can be improved following appropriate training before study initiation. However, several previous studies showed that OD cannot reach the recommended quality benchmarks of 90% diagnostic accuracy suggested by the AGSE PIVI[6] especially when applied in community practice.[22,30] Furthermore, although prediction of the polyp histology using OD techniques relies on validated classification systems, the optimal scale when using the i-Scan system remains

unknown. Indeed, previous studies found that OD could achieve the quality benchmarks when using NICE[31] and SIMPLE[29] classifications, but the WASP[32] classification performed poorly in combination with i-Scan. We found that the surveillance interval agreements between OD using NICE and Sano and pathology-based method could reach the recommended ASGE PIVI benchmark but were not significantly affected by the choice of NICE or Sano classifications. In contradistinction, OD did not achieve the required threshold when the WASP classification was used by endoscopists (Figure 1). In the sub-cohort of patients with adequate bowel preparation, none of optical classification system could reach the recommended benchmark. Further studies should investigate the recently proposed SIMPLE classification system.

Optical diagnosis has not gained widespread acceptance, especially in north America, due to concerns about making a wrong diagnosis, potential resulting medicolegal issues and assigning incorrect surveillance intervals to patients.[13] Society endorsement of a truly operator-independent resect and discard strategy would likely address many of these issues. Such strategy could be the proposed LBRD strategy, an adoption of artificial intelligence (AI)-assisted OD, or a combination of both. AI is a very promising method that has improved the detection rate and accuracy of OD of diminutive adenomatous polyps.[33,34] Nevertheless, this method still depends on the endoscopist's skill to present a clear and stable endoscopic image that centers on the polyp image in an optical chromoendoscopy mode. Although AI-assisted endoscopy could achieve better accuracy than OD for predicting the polyp histology,[33,34] our current study suggests that a dedicated polyp recognition technology may not be needed as a simple location-based strategy could confidently allocate surveillance interval in clinical practice, with a lower number of incorrect assignments made by endoscopists due to non-adherence to guidelines or low-confidence OD.[35] The strategy can also further be used in endoscopy settings that have no opportunity to update their endoscopy units with state-of-the-art AI-assisted systems, and to supplement the diagnostic decisions for any low-confidence diagnoses that occur with any other approach.

This study has several limitations. First, there was not a specific and validated training program for OD in i-Scan settings. Therefore, the endoscopists participated in an interactive training program that was previously validated based on the NBI and NICE classification using the still endoscopic images.[36] The endoscopists were also trained for the Sano and WASP classification systems by using additional images including the relevant polyp features' criteria used in those

systems. Second, the SIMPLE classification was validated in 2018 based on both i-Scan and NBI after the initiation of this study.[29,37] Therefore, we optically evaluated and documented polyp features based on the validated available classification systems. Third, although the location-based strategy showed promising results in allocation of post-polypectomy surveillance intervals, the low NPV of both the location-based strategy and OD to determine neoplastic diminutive rectosigmoid polyps indicates that these approaches are not yet ready for routine clinical implementation. Fourth, since the endoscopists used several optical polyp classifications, they could not be blind to their previous optical histological prediction. To best mitigate this problem, they were asked to perform the OD, first by using the WASP, second by using NICE, and finally by using Sano classification systems. A research assistant was present to show a laminated version of each classification system diagnostic criteria upon the endoscopists' request to avoid any bias. Fifth, the number of performed optical diagnoses and the level of expertise were not similar among all the endoscopists. Therefore, it was difficult to evaluate the effect of each endoscopist's performance on the final results of this study.

5. Conclusion

In conclusion, our study demonstrated very high (97%) post-polypectomy surveillance interval agreement between the LBRD strategy and the reference standard pathology using the 2020 USMSTF guideline. Moreover, the location-based strategy outperformed OD. Clinical implementation of the location-based strategy is likely safe and feasible but would require endorsement from endoscopy societies and further monitoring of its performance under routine clinical conditions in diverse settings such as community-based practices. The LBRD strategy could, however, mitigate the complexities of OD by being independent of operator experience and specialized equipment.

6. References

1. Djinbachian R, Dube AJ, von Renteln D. Optical Diagnosis of Colorectal Polyps: Recent Developments. *Curr Treat Options Gastroenterol* 2019; **17**(1): 99-114.
2. Gupta N, Bansal A, Rao D, et al. Prevalence of advanced histological features in diminutive and small colon polyps. *Gastrointest Endosc* 2012; **75**(5): 1022-30.
3. Lieberman D, Moravec M, Holub J, Michaels L, Eisen G. Polyp size and advanced histology in patients undergoing colonoscopy screening: implications for CT colonography. *Gastroenterology* 2008; **135**(4): 1100-5.
4. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2020; **158**(4): 1131-53 e5.
5. Chandran S, Parker F, Lontos S, Vaughan R, Efthymiou M. Can we ease the financial burden of colonoscopy? Using real-time endoscopic assessment of polyp histology to predict surveillance intervals. *Intern Med J* 2015; **45**(12): 1293-9.
6. 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**(3): 419-22.
7. Bisschops R, East JE, Hassan C, et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2019. *Endoscopy* 2019; **51**(12): 1155-79.
8. Rutter MD, East J, Rees CJ, et al. British Society of Gastroenterology/Association of Coloproctology of Great Britain and Ireland/Public Health England post-polypectomy and post-colorectal cancer resection surveillance guidelines. *Gut* 2020; **69**(2): 201-23.
9. East JE, Vleugels JL, Roelandt P, et al. Advanced endoscopic imaging: European Society of Gastrointestinal Endoscopy (ESGE) Technology Review. *Endoscopy* 2016; **48**(11): 1029-45.
10. Rastogi A, Rao DS, Gupta N, et al. 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**(3): 390-8.
11. Ignjatovic A, Thomas-Gibson S, East JE, et al. 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**(1): 128-33.
12. Dekker E, Houwen B, Puig I, et al. Curriculum for optical diagnosis training in Europe: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. *Endoscopy* 2020; **52**(10): 899-923.
13. Willems P, Djinbachian R, Ditisheim S, et al. Uptake and barriers for implementation of the resect and discard strategy: an international survey. *Endosc Int Open* 2020; **8**(5): E684-E92.
14. von Renteln D, Kaltenbach T, Rastogi A, et al. Simplifying Resect and Discard Strategies for Real-Time Assessment of Diminutive Colorectal Polyps. *Clin Gastroenterol Hepatol* 2018; **16**(5): 706-14.
15. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**(6 Suppl): S3-43.
16. Jass JR, Sobin LH, Morson BC. Histological typing of intestinal tumours. 2nd ed. Berlin ; New York: Springer-Verlag; 1989.

17. 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**(3): 599-607 e1.
18. JE IJ, 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**(6): 963-70.
19. Sano Y, Ikematsu H, Fu KI, et al. Meshed capillary vessels by use of narrow-band imaging for differential diagnosis of small colorectal polyps. *Gastrointest Endosc* 2009; **69**(2): 278-83.
20. Katagiri A, Fu KI, Sano Y, et al. Narrow band imaging with magnifying colonoscopy as diagnostic tool for predicting histology of early colorectal neoplasia. *Aliment Pharmacol Ther* 2008; **27**(12): 1269-74.
21. Ikematsu H, Matsuda T, Emura F, et al. 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.
22. Schachschal G, Mayr M, Treszl A, et al. Endoscopic versus histological characterisation of polyps during screening colonoscopy. *Gut* 2014; **63**(3): 458-65.
23. 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**(3): 844-57.
24. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ* 2015; **351**: h5527.
25. Bordet M, Bretagne JF, Piette C, et al. Reappraisal of the characteristics, management, and prognosis of intramucosal colorectal cancers and their comparison with T1 carcinomas. *Gastrointest Endosc* 2021; **93**(2): 477-85.
26. Paggi S, Rondonotti E, Amato A, et al. Resect and discard strategy in clinical practice: a prospective cohort study. *Endoscopy* 2012; **44**(10): 899-904.
27. Hong SN, Choe WH, Lee JH, et al. Prospective, randomized, back-to-back trial evaluating the usefulness of i-SCAN in screening colonoscopy. *Gastrointest Endosc* 2012; **75**(5): 1011-21 e2.
28. Royero G H. La cromoendoscopia virtual i-Scan y su aplicación en la detección y caracterización de los pólipos de colon %J Revista Colombiana de Gastroenterologia. 2017; **32**: 31-7.
29. Iacucci M, Trovato C, Daperno M, et al. Development and validation of the SIMPLE endoscopic classification of diminutive and small colorectal polyps. *Endoscopy* 2018; **50**(8): 779-89.
30. 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**(5): 887-95.
31. Pigo F, Bertani H, Manno M, et al. i-Scan high-definition white light endoscopy and colorectal polyps: prediction of histology, interobserver and intraobserver agreement. *Int J Colorectal Dis* 2013; **28**(3): 399-406.
32. Von Renteln D, Leduc R, Bouchard S, et al. A78 Comparison of the Nice, Sano, and Wasp Classifications for Optical Diagnosis of Small Colorectal Polyps. *Journal of the Canadian Association of Gastroenterology* 2020; **3**(Supplement_1): 92-3.
33. Byrne MF, Shahidi N, Rex DK. Will Computer-Aided Detection and Diagnosis Revolutionize Colonoscopy? *Gastroenterology* 2017; **153**(6): 1460-4 e1.
34. 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**(1): 94-100.

35. Djinbachian R, Dube AJ, Durand M, et al. Adherence to post-polypectomy surveillance guidelines: a systematic review and meta-analysis. *Endoscopy* 2019; **51**(7): 673-83.
36. 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**(3): 572-6.
37. Alaoui A, Oumedjbeur K, Djinbachian R, et al. A79 CLINICAL VALIDATION OF THE SIMPLE CLASSIFICATION FOR OPTICAL DIAGNOSIS OF DIMINUTIVE AND SMALL COLORECTAL POLYPS. *Journal of the Canadian Association of Gastroenterology* 2020; **3**(Supplement_1): 93-4.

Table 1 Demographic and clinical characteristics of 1117 patients and characteristics of the 921 detected diminutive polyps (1–5 mm).

Total number of patients	1117 (100)
Age, median (range), years	63.3 (45.0-80.9)
Male sex, n (%)	584 (52.3)
ASA class[a], n (%)	
1	494 (44.2)
2	539 (48.3)
3	83 (7.4)
Anticoagulant use, n (%)	245 (21.9)
Family history of CRC in first-degree relatives[b], n (%)	319 (28.6)
Colonoscopy characteristics[c], n (%)	
Colonoscopy indications	
Screening	343 (30.7)
FIT positive	38 (3.4)
Adenoma surveillance	228 (20.4)
CRC surveillance	39 (3.5)
Anaemia/bleeding	200 (17.9)
Diarrhoea	45 (4.0)
Other[d]	223 (20.0)
Caecal intubation during colonoscopy[e], n (%)	1051 (94.1)
Total Boston Bowel Preparation Scale ≥6[f], n (%)	983 (88.0)
Patients with no polyp, n (%)	469 (42.0)
Patients with ≥1 diminutive polyp, n (%)	482 (43.2)
Patients with only diminutive polyps, n (%)	388 (34.7)
Number of diminutive polyps, n/N (%)	921/1322 (69.7)
Anatomical location, n (%)	
Caecum	71 (7.7)
Ascending	159 (17.3)
Hepatic flexure	24 (2.6)
Transverse	141 (15.3)
Splenic flexure	12 (1.3)
Descending	121 (13.1)
Sigmoid	220 (23.9)
Rectum	173 (18.8)
Polyp size, mean (SD), mm	3.1 (1.3)
Histopathology results[g], n (%)	878 (96.3)
Hyperplastic	293 (31.8)
Tubular adenoma	401 (43.5)
Tubulovillous adenoma	12 (1.3)
Villous adenoma	2 (0.2)
Traditional serrated adenoma	3 (0.3)
Sessile serrated adenoma/polyp	27 (2.9)
Other benign lesions	149 (16.2)
Hyperplastic or mucosal protrusion	361 (39.2)

Neoplastic adenoma	445 (48.3)
Adenoma with advanced histology[h]	14 (1.5)
Adenoma with serrated histology[i]	30 (3.2)
Location-based neoplastic polyps	528 (57.3)
Location-based non-neoplastic polyps	393 (42.7)
Hyperplastic diminutive polyps in proximal colon[j]	78 (8.5)
Hyperplastic diminutive polyps in rectosigmoid colon[j]	215 (23.3)

[a]Missing = 1 (0.1%); [b]Missing = 1 (0.2%); [c]Missing = 1 (0.2%); [d]Other indications included surveillance due to family history of CRC, pre- and post-graft or organ donation, change in bowl habits such as constipation, post-polypectomy surveillance, screening for inflammatory diseases, ruling out diverticulitis, abdominal pain, celiac disease follow-up; [e]Missing = 2 (0.2%); [f]Missing = 8 (0.7%); [g]Missing = 34 (3.7%); [h]Including tubulovillous adenoma and villous adenoma (no polyp with high-grade dysplasia was found); [i]Including sessile serrated adenoma, traditional serrated adenoma; [j]Missing = 34 (3.5%).

FIT, faecal immunochemical test; CRC, colorectal cancer.

Table 2 Diagnostic properties of the location-based resect and discard strategy and optical diagnosis in patients with diminutive polyps (n = 921).

	Location-based strategy[a]	**NICE (i-Scan1)**	**NICE (i-Scan2)**	**Sano[b] (i-Scan2)**	**Sano (i-Scan3)**	**WASP (i-Scan2)**	**WASP (i-Scan3)**
Confidence level (high), n (%)	-	732 (79.5)[c]	725 (78.7)[d]	-	-	554 (60.2)	550 (59.7)
Hyperplastic, n (%)	-	483 (52.4)	492 (53.4)	481 (52.2)	487 (52.9)	367 (39.8)	383 (41.6)
Adenoma, n (%)	-	368 (40.0)	363 (39.4)	350 (38.0)	348 (37.8)	404 (43.9)	390 (42.3)
Serrated/sessile serrated adenoma/ polyps, n (%)	-	59 (6.4)	57 (6.2)	81 (8.9)[e]	76 (8.2)	141 (15.3)	139 (15.1)
Missing, n (%)	-	11 (1.2)	9 (1.0)	9 (1.0)	10 (1.1)	9 (1.0)	9 (1.0)
Hyperplastic polyps (pathology-based) in the proximal colon diagnosed with high confidence, n/N (%)	-	55/78 (70.5)	57/78 (73.1)	-	-	33/78 (42.3)	49/78 (62.8)
Diagnostic properties – all polyps[f], % (95% CI)							
Sensitivity	77.5 (73.4-81.3)	67.7 (63.1-72.1)	67.0 (62.4-71.4)	67.9 (63.4-72.3)	66.9 (62.4-71.3)	77.6 (73.5-81.4)	81.6 (77.5 to 85.1)
Specificity	73.4 (67.9-78.3)	80.8 (75.7-85.1)	81.8 (76.9-86.1)	80.1 (75.1-84.6)	80.5 (75.5-84.8)	61.6 (55.8-67.2)	68.2 (62.8 to 73.4)
PPV	81.6 (78.4-84.3)	84.3 (80.8-87.2)	84.9 (81.3-87.8)	83.8 (80.3-86.8)	83.8 (80.3-86.9)	75.4 (72.5-78.2)	77.5 (74.5 to 80.3)
NPV	68.2 (64.1-72.1)	62.2 (58.7-65.5)	62.1 (58.6-65.4)	62.2 (58.7-65.6)	61.7 (58.2-65.0)	64.5 (59.9-68.9)	73.4 (69.0 to 77.3)
Accuracy	75.9 (72.6-78.9)	72.9 (69.5-76.1)	72.9 (69.6-76.1)	72.8 (69.4-76.0)	72.3 (68.9-75.6)	71.3 (67.9-74.5)	75.9 (72.63 to 78.9)
Diagnostic properties – rectosigmoid polyps [g], % (95% CI)							
Sensitivity	70.0 (60.0-78.8)	69.0 (58.9-77.9)	59.0 (48.7-68.7)	58.6 (48.2-68.4)	58.6 (48.2-68.4)	59.0 (48.7-68.7)	NA

Specificity	67.3 (60. 6-73.5)	67.8 (61.0-74.0)	88.3 (83.2-92.3)	88.3 (83.2-92.3)	89.2 (84.3-93.0)	89.7 (84. 8-93.4)	100.0 (98.3-100.0)
PPV	50.0 (44.2-55.7)	50.0 (44.2-55.8)	70.2 (61.2-77.9)	69.9 (60.8-77.6)	71.6 (62.4-79.3)	72.8 (63.6-80.4)	NA
NPV	82.8 (77.8-86.8)	82.4 (77.5-86.4)	82.2 (78.4-85.4)	82.2 (78.4-85.4)	82.3 (78.6-85.5)	82.3 (78.6-85.5)	68.2 (68.2-68.3)
Accuracy	68.1 (62.7-73.3)	68.1 (62.7-73.3)	79.0 (74.0-83.3)	78.9 (74.0-83.3)	79.5 (74.6-83.9)	79.9 (75.0-84.2)	68.2 (62.8-73.4)

[a]For differentiating neoplastic from non-neoplastic rectosigmoid polyps; [b]Hyperplastic polyp (HP – MS I), sessile serrated adenomas/polyp (SSA/P – IIo), low-grade adenoma/tubular adenoma (TA – II), high-grade adenoma/tubulovillous adenoma/superficial cancer (TVA – IIIa)) and invasive cancer (IIIb); no confidence level was reported for MS classification; [c]Missing = 10 (1.1%); [d]Missing = 12 (1.3%); [e]Including type II0 and type IIIa, no type IIIb was detected; [f]For differentiating adenoma from hyperplastic polyps, including valid histopathology outcomes for all polyps; [g]For differentiating adenoma from hyperplastic polyps, including valid histopathology outcomes in rectosigmoid polyps.

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Table 3 Effect of incorrect diagnosis based on location-based resect and discard strategy on assignment of surveillance interval among patients with at least one diminutive polyp.

	n/N (%)
Patients with ≥1 diminutive polyp diagnosed	482 (100)
≥1 incorrect optical diagnosis based on location-based resect and discard strategy	208 (43.2)
Incorrect diagnosis did affect surveillance interval[a]	25/482 (5.2)
Incorrect diagnosis did not affect surveillance interval	183/482 (38.0)
Surveillance interval recommendations were based on (n=183):	
Family history of colorectal cancer	36 (19.7)
Inadequate bowel preparation	31 (16.9)
≥2 diminutive adenomas or ≥10 hyperplastic polyps ≤10 mm or normal mucosal variations	90 (49.2)
≥3 diminutive adenomas	5 (2.7)
Larger adenomas	21 (11.5)

[a]Among patients in whom an incorrect diagnosis would affect their next surveillance interval, 16 (64.0%) patients would be assigned a shorter and 9 (36.0%) a longer surveillance interval.

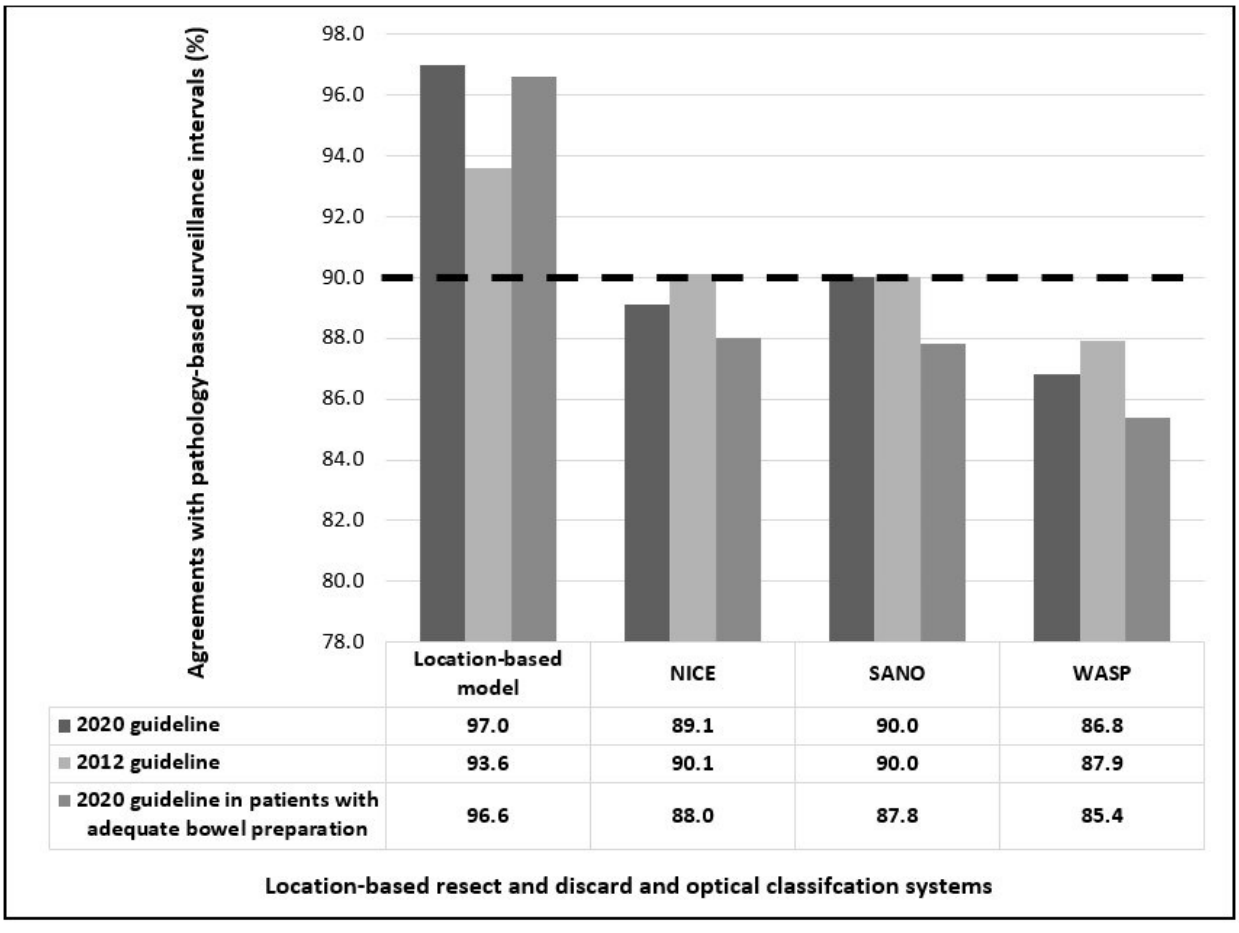


Figure 1 Agreement of surveillance intervals between pathology outcomes and the location-based resect and discard strategy and optical diagnosis in all patients with valid colonoscopies and in a sub-cohort of patients with adequate bowel preparation. The dash black line represents the 90% benchmark recommended by the ASGE PIVI statement.

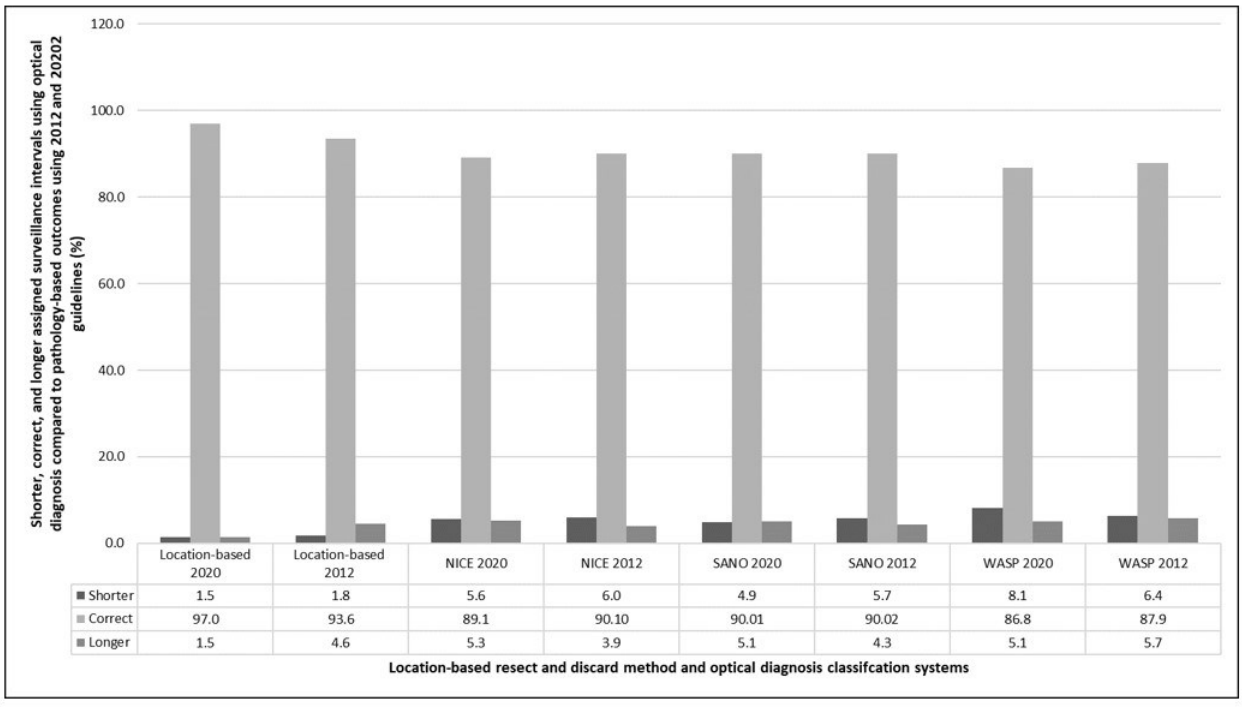


Figure 2 Proportion of correct and incorrect assigned surveillance intervals according to the location-based resect and discard model and optical diagnosis using different classification systems compared with histopathology outcomes as the reference standard in patients with diminutive polyps.

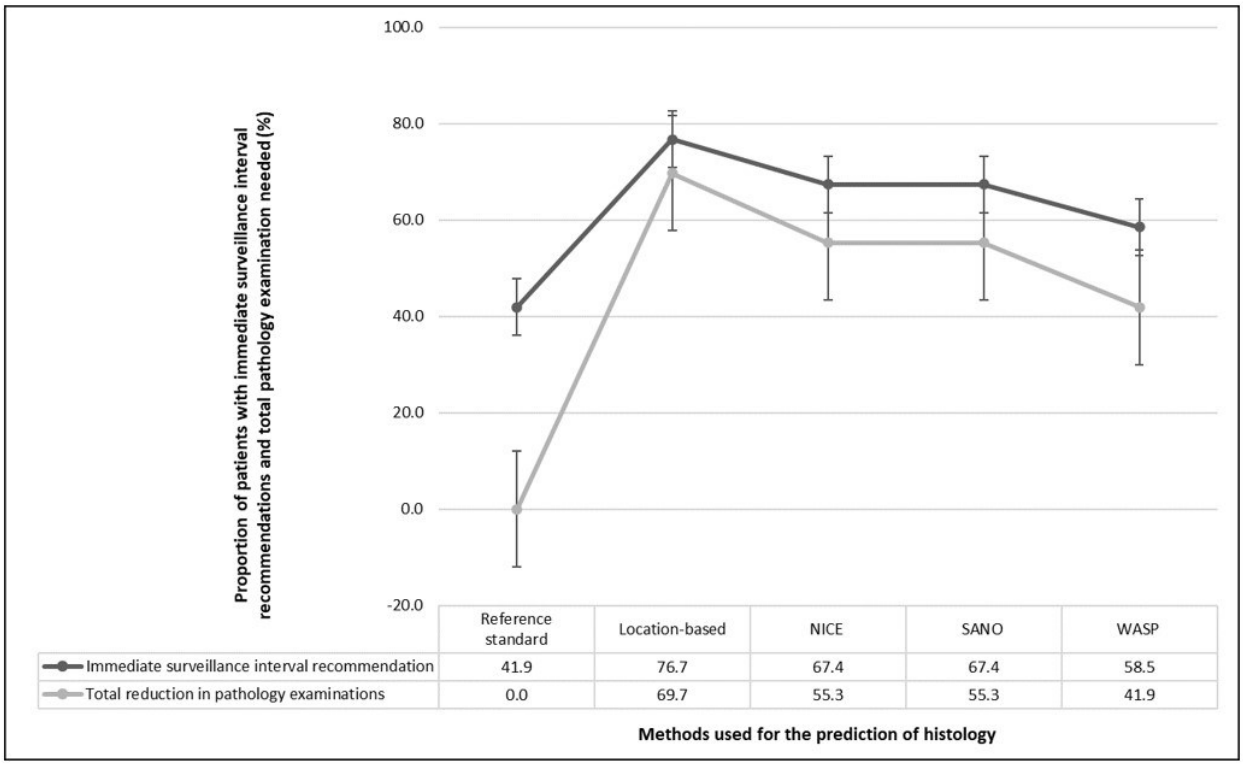


Figure 3 Proportion of patients who received immediate surveillance interval, and total reduction in pathology examinations following location-based resect and discard method and optical diagnosis.

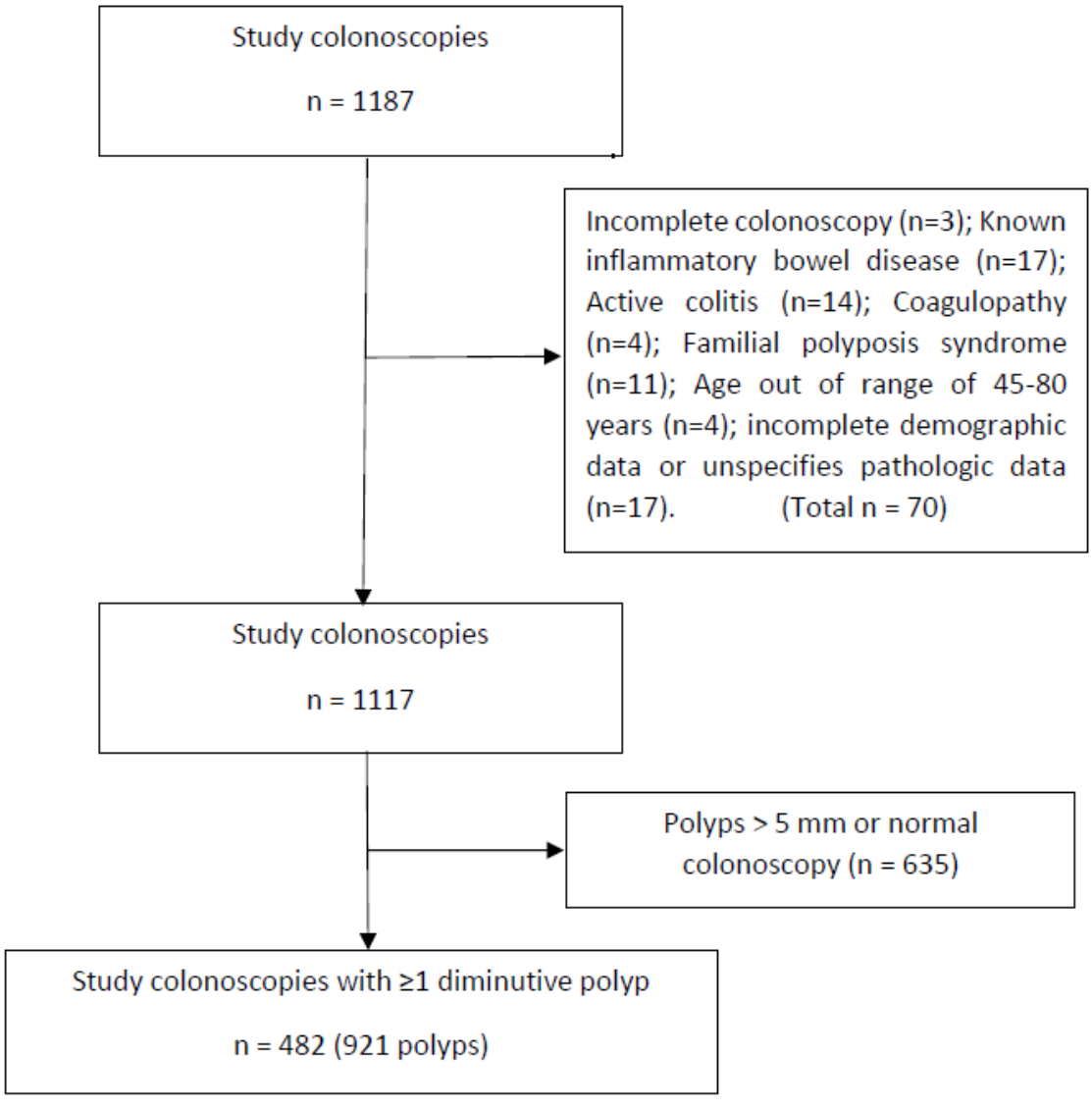
Supplementary Table 1 Comparison of surveillance interval agreements between optical diagnosis, location-based model, and histopathology outcomes – all colonoscopies[a].

		Surveillance intervals based on histopathology outcomes (years) (2012 USMSTF[b] guideline)					Surveillance intervals based on histopathology outcomes (years) (2020 USMSTF guideline)					Surveillance intervals based on histopathology outcomes (years)[c] (2020 USMSTF guideline)			
		1	3	5	10	Total	1	3	5	10	Total	3	5	10	Total
Surveillance intervals based on location-based model (years)	1	124	0	0	2	126	126	0	0	0	126	-	-	-	-
	3	0	100	0	1	101	0	98	3	0	101	98	2	8	108
	5	0	18	240	17	275	0	2	260	13	275	3	260	6	269
	10	0	12	19	537	568	0	8	6	554	568	0	13	554	567
Total		124	130	259	557	1070	126	108	269	567	1070	101	275	568	944
Surveillance intervals based on NICE classification system (years)	1	123	0	0	1	124	123	0	0	1	124	-	-	-	-
	3	1	50	3	9	63	1	41	12	9	63	41	12	25	78
	5	0	18	241	27	286	0	12	238	36	286	12	238	14	264
	10	0	32	11	516	559	2	25	14	518	559	9	37	518	564
Total		124	100	255	553	1032	126	78	264	564	1032	62	287	557	906
Surveillance intervals based on SANO classification system (years)	1	123	0	0	1	124	123	0	0	1	124	-	-	-	-
	3	1	50	3	10	64	1	42	11	10	64	42	11	25	78
	5	0	19	244	30	293	0	11	241	41	293	11	241	12	264
	10	0	31	8	513	552	2	25	12	513	552	10	42	513	565
Total		124	100	255	554	1033	126	78	264	565	1033	63	294	550	907
Surveillance intervals based on WASP classification system (years)	1	123	0	0	1	124	123	0	0	1	124	-	-	-	-
	3	1	50	3	11	65	1	42	11	11	65	42	11	25	78
	5	0	17	244	51	312	0	11	240	61	312	11	240	13	264
	10	0	33	8	490	531	2	25	13	491	531	11	61	492	564
Total		124	100	255	553	1032	126	78	264	564	1032	64	312	530	906

a: the concordant values have been highlighted; b: USMSTF = US Multi-Society Task Force; c: excluding patients with poor bowel preparation.

Supplementary Table 2 The surveillance interval agreement between pathology-based, location-based, and optical diagnosis-based assignment of surveillance intervals in the cohort of patients with only diminutive polyps (n=388).

	Pathology-based (2012 USMSTF guideline)	
	Agreement (n/N (%))	95% confidence interval
Location-based model	307/328 (93.6)	0.90-0.96
Optical diagnosis using NICE classification system	275/325 (84.6)	0.80-0.88
Optical diagnosis using Sano classification system	272/325 (84.0)	0.79-0.87
Optical diagnosis using WASP classification system	254/324 (78.4)	0.73-0.83



Supplementary Figure 1 Flowchart of the selection of patients with at least one diminutive polyp.

Chapter 3 – Article 3

Non-optical Polyp-Based Resect and Discard Strategy: A Prospective Study

Mahsa Taghiakbari[1], Célia Hammar[1,2], Mira Frenn[1,2], Roupen Djinbachian[1,3], Heiko Pohl[4,5], Erik Deslandres[1,6], Simon Bouchard[1,6], Mickael Bouin[1,6], Daniel von Renteln[1,6]

[1]Montreal University Hospital Research Center (CRCHUM), Montreal, Canada; [2]University of Montreal, Faculty of Medicine, Montreal, Canada; [3]Division of Internal Medicine, University of Montreal Hospital Center (CHUM), Montreal, Quebec, Canada; [4]Department of Veterans Affairs Medical Center, White River Junction, Vermont, United States; [5]Dartmouth Geisel School of Medicine and The Dartmouth Institute, Hanover, New Hampshire, United States; [6]Division of Gastroenterology, Montreal University Hospital Center (CHUM), Montreal, Canada

ABSTRACT

BACKGROUND & AIMS: Post-polypectomy surveillance intervals are currently determined based on pathology results. We aimed to evaluate a polyp-based resect and discard model that assigns surveillance intervals based solely on polyp number and size.

METHODS: Patients undergoing elective colonoscopies at the Montreal University Medical Center were enrolled prospectively. The polyp-based strategy was used to assign the next surveillance interval using polyp size and number. Surveillance intervals were also assigned using optical diagnosis for small polyps (<10 mm). The primary outcome was surveillance interval agreement between the polyp-based model, optical diagnosis, and the pathology-based reference standard using the 2020 U.S. Multi-Society Task Force guidelines. Secondary outcomes included the proportion of reduction in required histopathology evaluations and proportion of immediate post-colonoscopy recommendations provided to patients.

RESULTS: 944 patients (mean age 62.6 years, 49.3% male, 933 polyps) were enrolled. The surveillance interval agreement for the polyp-based strategy was 98.0% (95% confidence interval [CI], 0.97–0.99) compared with pathology-based assignment. Optical diagnosis-based intervals achieved 95.8% (95% CI, 0.94–0.97) agreement with pathology. When using the polyp-based strategy and optical diagnosis, the need for pathology assessment was reduced by 87.8% and 70.6%, respectively. The polyp-based strategy provided 93.7% of patients with immediate surveillance interval recommendations versus 76.1% for optical diagnosis.

CONCLUSION: The polyp-based strategy achieved almost perfect surveillance interval agreement compared with pathology-based assignments, significantly reduced the number of required pathology evaluations, and provided most patients with immediate surveillance interval recommendations.

Keywords: Colonoscopy; Colorectal Pathology; Colorectal Adenomas; Endoscopy; Surveillance.

1. Introduction

Screening colonoscopy and removal of detected polyps has been utilized to reduce Colorectal Cancer (CRC) morbidity and mortality.[1] The majority (90%) of polyps found during colonoscopies are less than 10 mm in size, with diminutive polyps (<5 mm) accounting for about 70–80%.[2,3] Most of these small polyps have been shown to be at very low risk for progression towards CRC. Advanced histology is found in only 1.7% of diminutive polyps and 10.1% of small polyps.[2,4] Histopathologic evaluation of small polyps can incur significant costs, therefore alternative modalities have been proposed, such as image-enhanced endoscopy-assisted optical polyp diagnosis (the "resect and discard" strategy).[5-7]

While optical diagnosis has achieved high level of accuracy in academic settings,[8-10] reports from general clinical practice have not been able to reproduce these results, with accuracies ranging between 75% and 85%, and surveillance interval assignment agreement with pathology of only 81%.[11,12] In a recent survey study, 59.9% of endoscopists reported that optical diagnosis was not feasible for clinical implementation, and 84.2% were not using the strategy in their current clinical practice.[13] Limitations of the resect and discard strategy included fear of making an incorrect optical diagnosis, assigning incorrect surveillance intervals, and training requirements.[13] Therefore, we aimed to develop a resect and discard model that did not require optical diagnosis to assign colonoscopy surveillance intervals. A retrospective study using this model, named the polyp-based resect and discard (PBRD) strategy, showed an 89.3% agreement with pathology-based surveillance recommendations.[14] This current study aimed to evaluate the PBRD model in a prospective clinical study comparing the strategy with optical polyp diagnosis using pathology-based surveillance interval recommendations as the reference standard.

2. Methods

Patients (aged 45–80 years) undergoing elective screening, surveillance, or diagnostic colonoscopies between May 2017 and December 2018 at the Centre Hospitalier de l'Université de Montréal (CHUM) were included. Exclusion criteria were known

inflammatory bowel disease, active colitis, coagulopathy, familial polyposis syndromes, American Society of Anesthesiologists classification score of >3, emergency colonoscopies, personal history of CRC, hospitalized patients, and presence of CRC during colonoscopy. The study was planned and conducted as a sub-study in patients enrolled in two prospective clinical studies (NCT04032912 and NCT03515343, respectively). The study protocol and data collection were approved by the local institutional research board as an amendment to the two prospective clinical studies (17.135 and 16.367, respectively).

2.1 Colonoscopy Procedures

Colonoscopy procedures were performed as per the standard of care. Adequate bowel preparation was determined by a Boston Bowel Preparation Score (BBPS) of ≥6. Location, size, and morphology according to the Paris classification were documented for each polyp. All polyps were removed and sent for histopathology evaluation. Polyps 1–10 mm were optically diagnosed using either i-Scan or Optivista image-enhanced endoscopy (Pentax, Montvale, NJ, USA) and classified using the Narrow-band imaging International Colorectal Endoscopic (NICE) classification system.[6,15] Endoscopist level of confidence (low or high) in optical histology prediction was documented. Endoscopists then used the PBRD strategy to assign the next surveillance interval immediately after colonoscopy (real-time application). Then, a research assistant (MT) used the PBRD strategy (post hoc) to determine whether endoscopists had deviated from the intended PBRD strategy and assessed the PBRD model results when used without deviations.

2.2 The PBRD Model

The PBRD strategy was developed by the research group and previously tested in a pilot study.[14] There was no overlap between the cohort enrolled in the pilot study and the cohort presented herein. The PBRD uses number and size of polyps, and first-degree family history of CRC to predict the next surveillance interval. At the time of the study, the 2012 U.S. Multi-Society Task Force (USMSTF) guidelines[16] were the most current guidelines used to develop the PBRD strategy (**Table 1**). With the publication of the

updated 2020 USMSTF guidelines[17] during the course of the study, we adapted the PBRD model to reflect those changes through consensus between two researchers (RD and DvR), and tested its performance post hoc (**Table 1**). Since the 2020 guidelines are the most contemporaneous, the 2020-based analysis was used as the primary outcome of the study. Pathology-based surveillance intervals were therefore determined using 2012 or 2020 USMSTF guidelines as appropriate.[16,17] In cases of multiple recommended intervals (for example, 7–10 years), the longest interval was chosen to compare the strategies.

2.3 Study Outcomes

The primary outcome was the agreement between PBRD-based surveillance intervals and pathology-based surveillance intervals and agreement between updated PBRD-based surveillance intervals and pathology-based surveillance intervals. Secondary endpoints were: agreement between optical diagnosis-based surveillance intervals and pathology-based intervals; agreement between real-time endoscopist allocation of intervals based on PBRD compared with pathology-based intervals; proportion of immediate post-colonoscopy surveillance recommendations provided to patients based on both PBRD (real-time and post hoc) and optical diagnosis; proportion of required histopathology evaluations when using PBRD and optical diagnosis. Other secondary outcomes included the proportion of patients with findings that could have been provided with immediate surveillance interval recommendations: no polyps detected; inadequate bowel preparation; polyps sized 1–10 mm that were all optically diagnosed with high confidence (for the optical diagnosis strategy); patients fitting scenarios 1, 2, 3, and 6 (for the PBRD strategy) (**Table 1**). Polyps undergoing low-confidence optical diagnosis, polyps >10 mm in size, and all polyps in patients fitting scenarios 4 and 5 (for the PBRD strategy) required histopathology evaluation.

2.4 Statistical Analysis

Patient, procedure, and polyp characteristics were presented as crude numbers and frequency for categorical variables, and mean with standard deviation (SD) or median

(range) for continuous variables. Agreements between the PBRD model, optical diagnosis, and pathology-based surveillance recommendations were presented as proportions with two-tailed 95% confidence interval (CI). For secondary outcomes, proportional estimates with two-tailed 95% CI were presented. A chi-squared test or a two-tailed Fisher's exact test was used to compare proportions. SPSS version 26.0 (IBM Corp., Armonk, New York, USA) and MedCalc version 19.4 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org) were used for analyses.

3. Results

3.1 Patient and Polyp Characteristics

A total of 1157 patients were screened, and 944 patients with 933 polyps were included in the final analysis (mean age 62.6 [SD 8.6] years; 49.3% male) (**Supplementary Figure 1)**. Most colonoscopies were performed for screening and surveillance. Among all detected polyps, 819 (87.8%) were either diminutive or small (1–9 mm). **Table 2** shows the details of patient, procedure, and polyp characteristics.

3.2 Polyp-Based Resect and Discard Strategy Surveillance Intervals

The PBRD strategy based on the 2020 guidelines reached 98.0% (95% CI, 0.97–0.99) agreement with pathology-based surveillance intervals (**Figure 1**). Based on the 2012 guidelines, surveillance interval agreement between real-time PBRD strategy and pathology was 76.4% (95% CI, 0.74–0.79). Endoscopists using the PBRD strategy assigned shorter and longer surveillance intervals in 15.4% and 8.3% of patients, respectively. When applied post hoc, the PBRD strategy based on the 2012 guidelines reached 90.7% (95% CI, 0.89–0.92) agreement with pathology-based recommendations, with shorter and longer intervals assigned in 5.8% and 3.5% of patients, respectively. The proportion of endoscopist assigned surveillance intervals that adhered to pathology-based intervals was significantly lower than those assigned post-hoc using the same strategy ($P < 0.0001$) (**Table 3**). None of the patients that should have received shorter surveillance intervals through the post-hoc PBRD model had a polyp with advanced histology. Only 3/145

patients that should have been assigned to shorter surveillance intervals by endoscopists had polyps with advanced histology. Deviations from the strategy decreased as the study progressed (**Figure 2**).

3.3 Optical Diagnosis-Based Surveillance Intervals

A total of 842 (90.2%) polyps ≤10 mm were optically diagnosed using NICE; of those, 648 (69.5%) were classified with high confidence (**Table 2**). The agreement between surveillance intervals assigned by optical diagnosis and pathology-based intervals using 2012 guidelines was 95.8% (95% CI, 0.94–0.97) (**Figure 1**). The agreement with pathology for surveillance intervals assigned by optical diagnosis was significantly higher than that for both the PBRD strategy used by endoscopists ($P < 0.0001$) and the PBRD strategy calculated post-hoc based on 2012 ($P < 0.0001$). **Supplementary Table 1** shows allocation of surveillance intervals between optical diagnosis and pathology.

3.4 Histopathology Evaluations and Immediate Surveillance Recommendations

When using the standard clinical approach, 50.6% of patients could have been given an immediate surveillance recommendation post-colonoscopy. The PBRD strategy (based on 2020 guidelines) and optical diagnosis would have allowed for immediate surveillance interval recommendation in 93.7% (95% CI, 0.92–0.95, and 76.1% (95%CI 0.73-0.79) of patients, respectively (**Figure 3**). The PBRD strategy reduced 87.8% of histopathology evaluations compared with 70.6% for optical diagnosis (**Figure 4**).

4. Discussion

Our study found that surveillance interval assignment using the PBRD strategy based on the 2020 USMSTF guidelines reached 98.0% agreement with pathology. This agreement was significantly higher compared to optical diagnosis-based strategies. In contrast to

optical diagnosis, the use of the PBRD strategy is independent of operator skill, leading to increased reproducibility in routine endoscopic practice.

Interestingly, we found that when the PBRD strategy was used in real-time by endoscopists, adherence to guideline recommendations was lower; endoscopists chose a different surveillance interval than the PBRD strategy in 20% of patients, possibly due to clinical information not reflected in the strategy, such as second-degree relatives with CRC or other individual factors. Our findings also reflect previously described practice patterns where endoscopists often assigned shorter surveillance intervals for low-risk lesions and normal colonoscopies, with highly variable but often low (<50%) adherence to guidelines. Reasons for non-adherence stated in the literature included disagreement with guidelines, inadequate or suboptimal bowel preparation, and concern for missed polyps.[18-20] These factors potentially played a role in endoscopist deviations from the PBRD strategy in our study. Another explanation to these deviations could be the learning curve for PBRD implementation. We found that as the study progressed, the percentage of deviations from the PBRD strategy decreased (**Figure 2**).

Agreement between pathology-based and post-hoc allocation of surveillance intervals using the PBRD strategy based on 2020 USMSTF guidelines was significantly higher than the agreement between pathology-based and optical-based allocation of surveillance intervals (98.0% [95% CI, 0.97–0.99] vs. 95.8% [95% CI, 0.94–0.97]; $P = 0.005$). Additionally, the agreement between optical diagnosis-based surveillance intervals and pathology surpassed the American Society for Gastrointestinal Endoscopy Preservation and Incorporation of Valuable endoscopic Innovations 90% benchmark.[5] However, agreement between surveillance interval assignments using real-time application of PBRD by endoscopists, and pathology was significantly lower than for optical diagnosis. In our study, 70% of polyps were optically classified with high confidence, similar to the rates reported by other studies.[21] Increasing the rate of high-confidence optical diagnosis would contribute to the acceptance of this technique in routine endoscopic practice, particularly for non-academic endoscopists. However, endoscopists are often reluctant to use optical diagnosis due to concerns of incorrect diagnosis, inappropriate surveillance interval assignment, and fear of potential medicolegal repercussions.[13] As our adaptation of the PBRD strategy to reflect the updated 2020 USMSTF guideline resulted in a

significantly higher agreement compared with the 2012-based PBRD model (98.0% [95% CI, 0.97–0.99] vs. 90.7% [95% CI, 0.89–0.92]; $P < 0.0001$), we believe that the PBRD strategy may be a safe alternative that can be easily applied by endoscopists pending further research confirming efficacy in real-time endoscopic practice, and Gastroenterology society endorsements. The PBRD strategy and optical diagnosis resulted in significant reductions in required histopathology evaluations, and increased the percentage of patients with same-day surveillance interval assignment. A significant proportion of post-colonoscopy colorectal cancers (PCCRCs) are due to administrative or decision-making errors.[22] Fail-safe mechanisms are therefore needed to ensure the assignment of an appropriate surveillance interval during the index session for follow-up examination. For instance, histopathology might not be followed up adequately, or patients might fail to receive their surveillance interval after pathology results are available. This would exacerbate loss to follow-up and increase the chance of PCCRC. The PBRD strategy could offer a simple solution for endoscopists to communicate the appropriate time for the next surveillance colonoscopy without requiring histopathology evaluation.

Another advantage of the PBRD strategy is that very high agreement with pathology-based surveillance intervals can be achieved without any specialized training, skill, or dedicated equipment. The PBRD strategy might be easier to implement and may address fears cited by endoscopists. As the fear of discarding polyps with advanced histology remains a significant concern and could limit the widespread adoption of resect and discard strategies, revised versions of PBRD could exclude polyps with morphology of potentially advanced lesions (e.g., Paris IIc or III). Furthermore, it might be beneficial to limit the use of the PBRD strategy to diminutive polyps only, which would reduce the risk of assigning polyps with high-grade dysplasia or serrated adenomas to longer surveillance intervals, as advanced pathology occurs more frequently in polyps of 6–9 mm. Notably, the post hoc application of the PBRD strategy did not result in discarding any polyp with advanced histology in our study. Limiting this strategy to 1–3 mm polyps could also be feasible, especially when optical diagnosis is not possible and pathology examination to determine the histology of these polyps not reliable. Approaches to replace pathology for these polyps are likely safe as a recent study showed that advanced histologic features in diminutive polyps did not contribute towards metachronous CRC.[23]

The emergence of new modalities such as artificial intelligence (AI)-assisted classification could provide an alternative to the proposed approach in the future. However, the accuracy of AI-based optical diagnosis in broader clinical practice with different endoscopists, platforms, and settings remains to be evaluated, with widespread clinical implementation far from reality. Furthermore, it is unlikely that every endoscopy unit could implement this cutting-edge technology immediately or at all once available. Therefore, the PRBD strategy could be used as a bridge or complementary system to AI. The current strategy of resection and histopathologic analysis of all polyps is associated with high costs. Previous studies estimated that the annual cost saving in the US population following the adoption of a resect and discard policy for diminutive polyps ranges from US$ 33 million to $1 billion annually.[24] By reducing such costs, healthcare systems could increase efficiency and reallocate savings to other resources in CRC prevention, such as screening in younger age groups.

Several limitations should be discussed. Patient recruitment was at a single academic center, limiting the generalizability of our results. Future research should assess PBRD in multicentered studies and community-based practices. The PBRD strategy could be improved by considering other important clinical factors, such as in-depth family and personal history of CRC and/or polyps, suboptimal bowel preparation score (e.g., BBPS of 5 or 6), or offering more granular choices to clinicians. Furthermore, results of this study may have been improved if PBRD was limited to diminutive or 1–3 mm polyps only, due to the low prevalence of advanced histology in such polyps at the expense of lower proportion of patients with same day surveillance interval assignment and higher proportion of required pathology examinations.[4]

5. Conclusion

In conclusion, the PBRD strategy reached 98.0% agreement with surveillance intervals assigned through pathology using the 2020 USMSTF guidelines. Performance with the 2012 guidelines was lower when implemented correctly but still surpassed the 90% benchmark. Optical diagnosis also performed above the 90% benchmark in our study.

Therefore, the PBRD strategy may be a feasible alternative to resect and discard that can be used without specialized equipment, training, or optical diagnosis skills.

6. References

1. Zhang R, Zheng Y, Mak TW, et al. Automatic Detection and Classification of Colorectal Polyps by Transferring Low-Level CNN Features From Nonmedical Domain. *IEEE J Biomed Health Inform* 2017; **21**(1): 41-7.
2. von Renteln D, Pohl H. Polyp Resection - Controversial Practices and Unanswered Questions. *Clin Transl Gastroenterol* 2017; **8**(3): e76-e.
3. Vleugels JLA, Hazewinkel Y, Fockens P, Dekker E. Natural history of diminutive and small colorectal polyps: a systematic literature review. *Gastrointest Endosc* 2017; **85**(6): 1169-76 e1.
4. Butterly LF, Chase MP, Pohl H, Fiarman GS. Prevalence of clinically important histology in small adenomas. *Clin Gastroenterol Hepatol* 2006; **4**(3): 343-8.
5. 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**(3): 419-22.
6. Committee AT, Abu Dayyeh BK, Thosani N, 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**(3): 502 e1- e16.
7. Schachschal G, Mayr M, Treszl A, et al. Endoscopic versus histological characterisation of polyps during screening colonoscopy. *Gut* 2014; **63**(3): 458-65.
8. Kaltenbach T, Rex DK, Wilson A, et al. Implementation of optical diagnosis for colorectal polyps: standardization of studies is needed. *Clin Gastroenterol Hepatol* 2015; **13**(1): 6-10 e1.
9. Pohl H, Bensen SP, Toor A, et al. Quality of optical diagnosis of diminutive polyps and associated factors. *Endoscopy* 2016; **48**(9): 817-22.
10. Glover B, Patel N, Ashrafian H, Teare J. Diagnostic accuracy of i-scan image enhancement for real-time endoscopic diagnosis of small colorectal polyps: a meta-analysis. *Therap Adv Gastroenterol* 2018; **11**: 1756284818814948.
11. van den Broek FJ, van Soest EJ, Naber AH, et al. Combining autofluorescence imaging and narrow-band imaging for the differentiation of adenomas from non-neoplastic colonic polyps among experienced and non-experienced endoscopists. *Am J Gastroenterol* 2009; **104**(6): 1498-507.
12. Kuiper T, Marsman WA, Jansen JM, et al. Accuracy for optical diagnosis of small colorectal polyps in nonacademic settings. *Clin Gastroenterol Hepatol* 2012; **10**(9): 1016-20; quiz e79.
13. Willems P, Djinbachian R, Ditisheim S, et al. Uptake and barriers for implementation of the resect and discard strategy: an international survey. *Endosc Int Open* 2020; **8**(5): E684-E92.
14. Duong A, Bouin M, Leduc R, et al. A7 the Polyp-Based Resect-and-Discard Strategy. *Journal of the Canadian Association of Gastroenterology* 2019; **2**(Supplement_2): 15-6.
15. Patrun J, Okresa L, Ivekovic H, Rustemovic N. Diagnostic Accuracy of NICE Classification System for Optical Recognition of Predictive Morphology of Colorectal Polyps. *Gastroenterol Res Pract* 2018; **2018**: 7531368.
16. 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**(3): 844-57.
17. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2020; **158**(4): 1131-53 e5.
18. Goodwin JS, Singh A, Reddy N, Riall TS, Kuo YF. Overuse of screening colonoscopy in the Medicare population. *Arch Intern Med* 2011; **171**(15): 1335-43.
19. van Heijningen EM, Lansdorp-Vogelaar I, Steyerberg EW, et al. Adherence to surveillance guidelines after removal of colorectal adenomas: a large, community-based study. *Gut* 2015; **64**(10): 1584-92.
20. Djinbachian R, Dube AJ, Durand M, et al. Adherence to post-polypectomy surveillance guidelines: a systematic review and meta-analysis. *Endoscopy* 2019.
21. 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**(2): E140-E5.
22. Kaminski MF. Avoiding a plane crash with colonoscopy. *Endoscopy* 2022; **54**(03): 278-80.
23. Tang Y, Anandasabapathy S, Richards-Kortum R. Advances in optical gastrointestinal endoscopy: a technical review. *Mol Oncol* 2021; **15**(10): 2580-99.
24. Kandel P, Wallace MB. Should We Resect and Discard Low Risk Diminutive Colon Polyps. *Clin Endosc* 2019; **52**(3): 239-46.

Table 1 The Polyp-Based Resect and Discard (PBRD) Strategy.

Scenario	Rule	Surveillance interval recommendation based on 2012 guidelines, years	If family history of CRC (first-degree relative)
1	No polyp	10	5
2	1–2 diminutive polyps (Largest polyp max. 5 mm)	10	5
3	1–3 small polyps (All polyps 1–9 mm and the largest polyp max. <10 mm)	5	5
4	≥4 polyps, any size	Follow-up pathology results	-
5	At least 1 polyp ≥10 mm	Follow-up pathology results	-
6	Insufficient or inadequate bowel preparation	1	-
7	Unclear	-	-
Scenario	**Rule**	**Surveillance interval recommendation based on 2020 guidelines, years**	**If family history of CRC (first-degree relative)**
1	No polyp	10	5
2	1–3 diminutive polyps; or 2 diminutive polyps and 1 small polyp	10	5
3	1–2 small polyps exclusively	10	5
4	>3 polyps, any size, or >2 polyps 6–9 mm	Follow-up pathology results	–
5	≥1 polyp ≥10 mm	Follow-up pathology results	–
6	Insufficient or inadequate bowel preparation	1	1

CRC, colorectal cancer

Table 2 Patient, Procedure, and Polyp Characteristics[a].

Patients, n	**944**
Age, mean (SD), years	62.6 (8.6)
Male sex, n (%)	465 (49.3)
Family history of CRC,[b] n (%)	
No	682 (72.2)
Yes	259 (27.4)
Colonoscopy indication, n (%)	
Screening	299 (31.7)
FIT+	39 (4.1)
Adenoma surveillance	206 (21.8)
Anemia/bleeding	158 (16.7)
Diarrhea	28 (3.0)
Other	214 (22.7)
Procedures	
Bowel preparation quality, n (%)	
Adequate	851 (90.1)
Inadequate[c]	93 (9.9)
Cecal intubation rate, n (%)	902 (95.6)
Polyp detection rate[d], %	53.7%
Adenoma detection rate[d], %	36.4%
Polyps, n	**933**
Polyp size, mean (SD), mm	5.8 (8.3)
Polyp size, n (%)	
≤5 mm	689 (73.8)
6–9 mm	130 (13.9)
≥10 mm	114 (12.2)
Histopathology, n (%)	
Hyperplastic polyp	274 (29.4)
Tubular adenoma	468 (50.2)
Villous adenoma	36 (3.9)
Traditional serrated adenoma	1 (0.1)
Sessile serrated adenoma/polyp	38 (4.1)
Other	103 (11.0)

High-grade dysplasia	13 (1.4)
Tubular adenoma with HGD	3/13 (23.1)
Villous adenoma with HGD	10/13 (76.9)
Optical histology prediction based on NICE classification	842/933 (90.2)[e]
Non-neoplastic	345 (41.0)
Neoplastic	497 (59.0)
High-confidence optical diagnosis	648 (69.5)

CRC, colorectal cancer; FIT, fecal immunochemical test; HGD, high-grade dysplasia; NICE, Narrow-band imaging International Colorectal Endoscopic; SD, standard deviation.

[a]Patients with at least 1 ≤10 mm polyp.

[b]Unknown family history of CRC= 3 (0.3%).

[c]Defined as Boston Bowel Preparation Score <6.

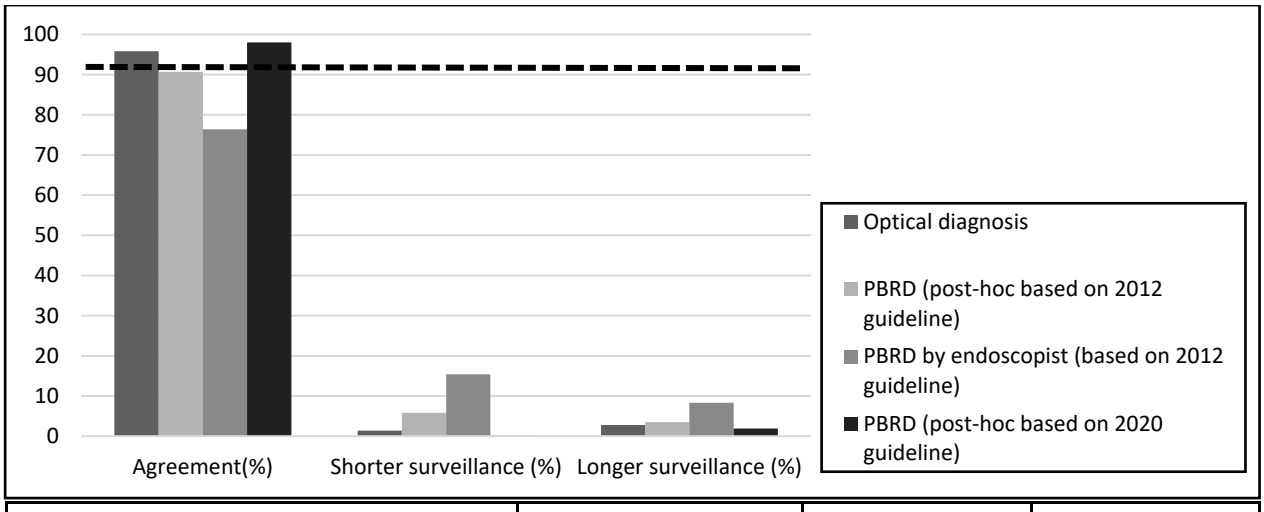
[d]Defined as percentage of patients where at least 1 polyp/adenoma was found.

[e]All polyps were ≤10 mm.

Table 3 Concordance Between Endoscopist Polyp-Based Resect and Discard (PBRD) Strategy and Post Hoc PBRD Surveillance Interval Assignment Compared with Histopathology[a].

Endoscopist PBRD[a]	Post-hoc PBRD[a]			*P*[*]
	Shorter	Correct	Longer	
Shorter	54	89	3	<0.0001
Correct	1	714	3	
Longer	0	51	28	

[a]Surveillance intervals based on the 2012 guideline.
PBRD, polyp-based resect and discard.



Strategy	Agreement, % (95% CI)	Shorter surveillance, % (95% CI)	Longer surveillance, % (95% CI)
Optical diagnosis (vs reference standard based on 2012 guideline)	95.8 (0.94–0.97)	1.4 (0.007–0.02)	2.8 (0.02–0.04)
PBRD (post-hoc vs reference standard based on 2012 guideline)	90.7 (0.89–0.92)	5.8 (0.04–0.07)	3.5 (0.02–0.05)
PBRD (by endoscopist vs reference standard based on 2012 guideline)	76.4 (0.74–0.79)	15.4 (0.13–0.18)	8.3 (0.07–0.10)
PBRD (post-hoc vs reference standard based on 2020 guideline)	98.0 (0.97–0.99)	0.1 (0–0.006)	1.9 (0.01–0.03)

Figure 1 Surveillance agreement of optical diagnosis and polyp-based resect and discard (PBRD) strategy compared with histopathology. The dashed black line represents the 90% agreement of surveillance interval.

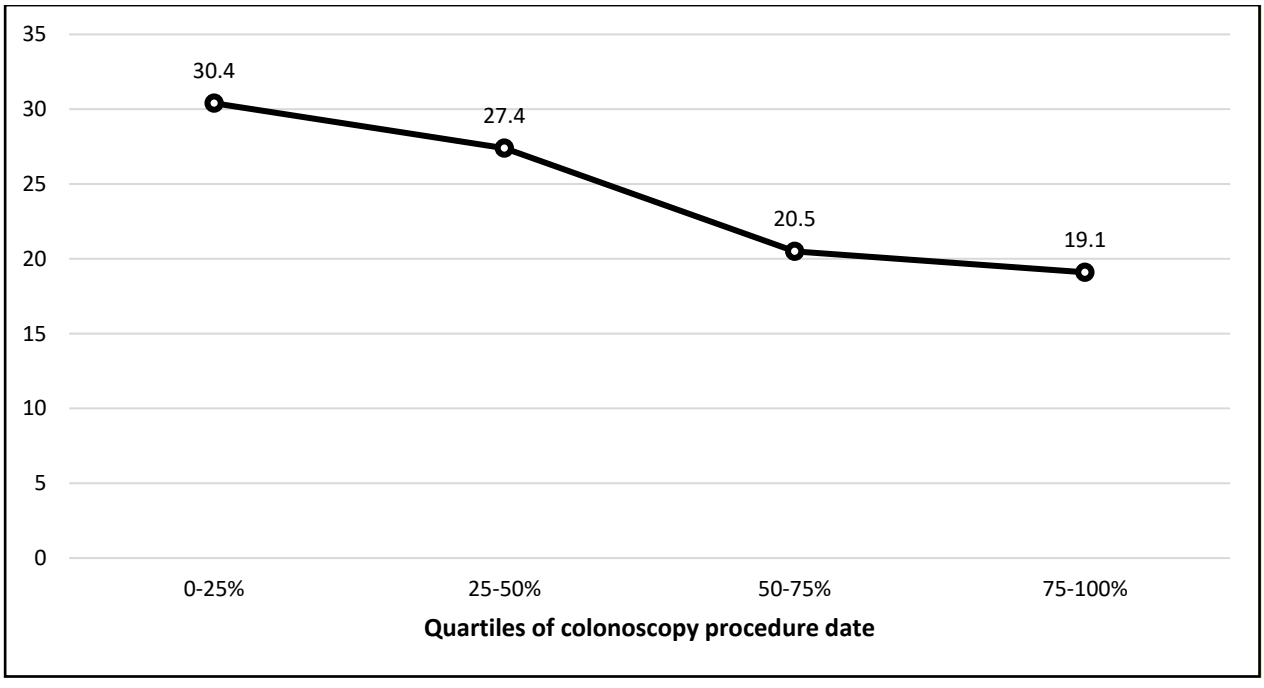
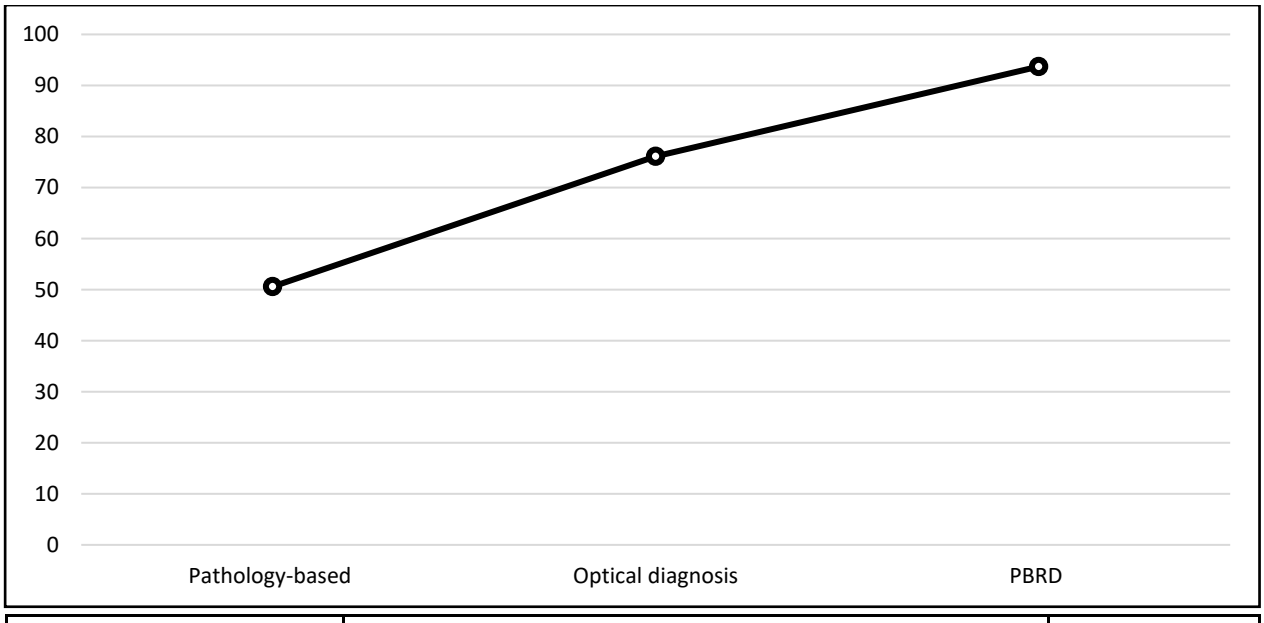
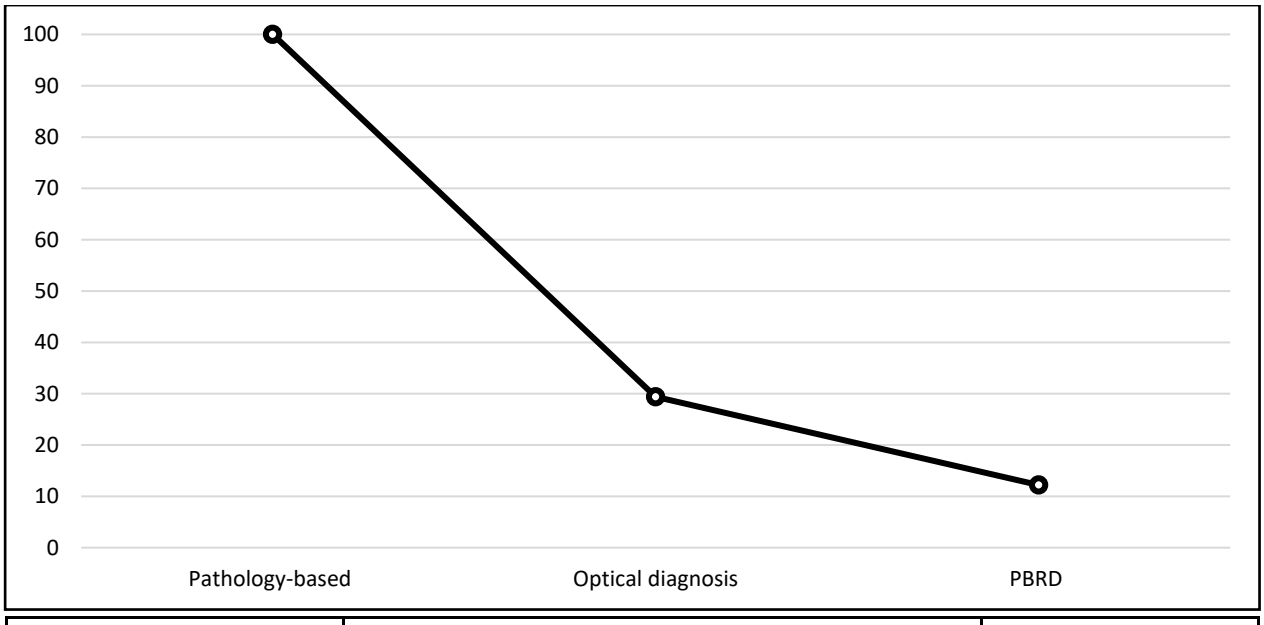


Figure 2 Proportion of the deviation from the polyp-based resect and discard strategy by endoscopists during the study by quartiles of procedure date.



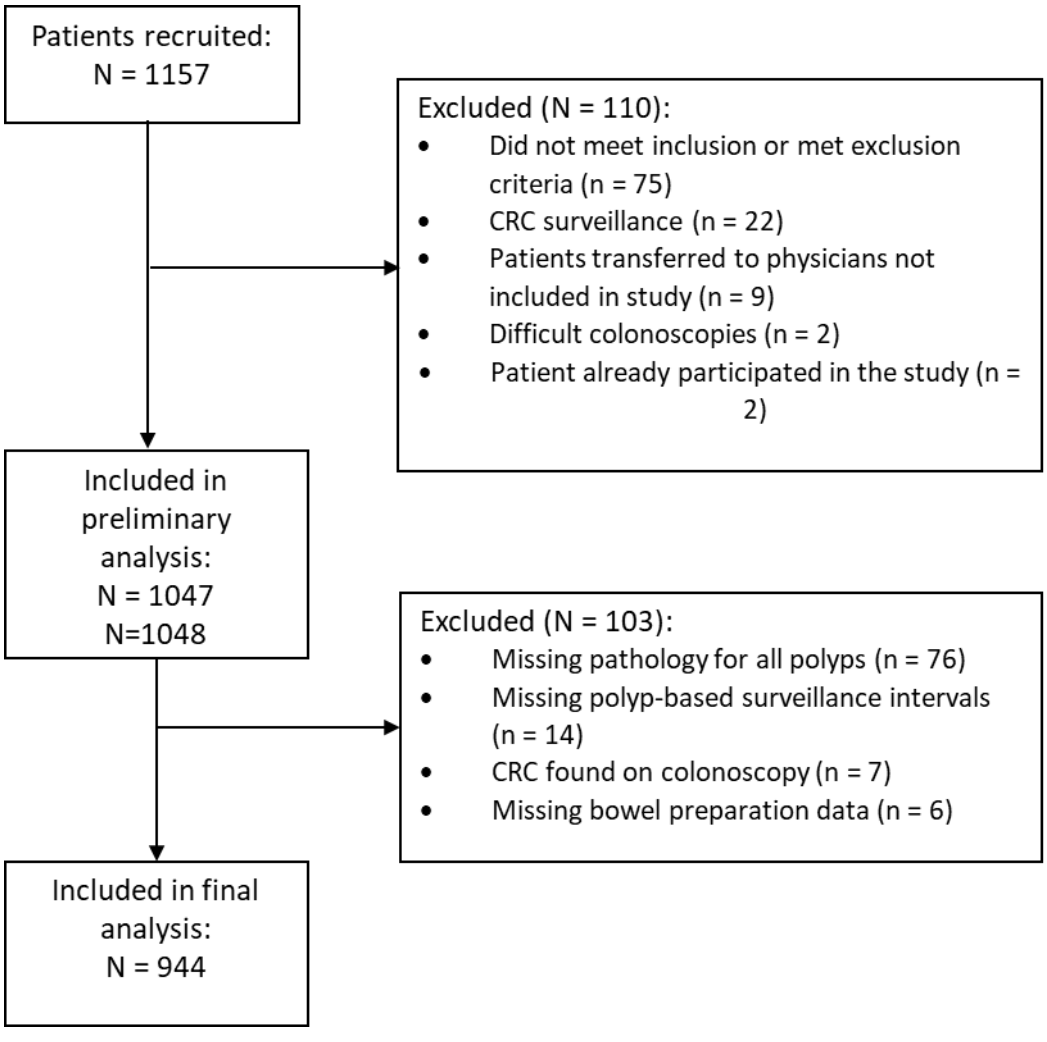
Strategy	Immediate surveillance interval recommendations, %	95% CI
Pathology based	50.6	0.47–0.54
Optical diagnosis	76.1	0.73–0.79
PBRD	93.7	0.92–0.95

Figure 3 Proportion of immediate surveillance interval recommendations provided to patients based on pathology-based outcomes, polyp-based resect and discard (PBRD) strategy, and optical diagnosis.



Strategy	Pathology examinations required, %	95% CI
Pathology based	REFERENCE	REFERENCE
Optical diagnosis	29.4	0.26–0.32
PBRD	12.2	0.10–0.15

Figure 4 Proportion of pathology examinations required based on pathology-based outcomes, PBRD strategy, and optical diagnosis. The black bars represent the 95% CI.



Supplementary Figure 1 Flowchart of the selection of the study subjects.

SECTION Ⅱ

Chapter 4: Endoscopic Size Measurement of Colorectal Polyps: A Review of Methods and Clinical Implications

Chapter 5: Measuring Colorectal Polyp Size Using a Virtual Scale Function During Endoscopies: A Clinical Pilot Study

Chapter 4 – Article 4

Endoscopic Size Measurement of Colorectal Polyps: A Review of Methods and Clinical Implications

Mahsa Taghiakbari[1,2], Roupen Djinbachian[1,3], Abdelhakim Khellaf[1,4], Daniel von Renteln[1,3]

[1] University of Montreal, Montreal, Quebec, Canada; [2]University of Montreal Hospital Research Center (CRCHUM), Montreal, Quebec, Canada; [3]Division of Gastroenterology, University of Montreal Hospital Center (CHUM), Montreal, Quebec, Canada; [4]Department of Anatomopathology, University of Montreal Hospital Center (CHUM), Montreal, Quebec, Canada

ABSTRACT

Estimating the size of colorectal polyps is crucial for determining the risk of advanced pathology and guiding clinical management. This review aimed to assess the available measurement modalities and recent technological advancements in polyp size measurement. A comprehensive search was conducted in Medline, EMBASE and PubMed from 1980 to 2023, revealing that there is currently no gold standard for measuring polyp size during colonoscopy. Endoscopists' size estimation and pathology size measurement show significant variation and uncertainty. Various calibrated and uncalibrated tools exist for size measurement, but their limited usage is attributed to availability, practicality, and procedural costs. Recent developments in artificial intelligence and laser-based systems offer promising solutions, providing adaptive scales or direct measurements with a simple button press during colonoscopy. Preclinical and clinical studies have demonstrated the potential of these methods to enhance polyp size estimation in real-time colonoscopies.

Keywords: Colonoscopy; Polyp size measurement; Biopsy forceps; Virtual scale; Artificial intelligence.

1. Introduction

Colonoscopy is a reliable and safe screening modality for detecting and removing colorectal cancer (CRC) precursors. Post-colonoscopy management is determined by polyp multiplicity, size, and histology.[1] According to the 2020 US Multi-Society Task Force (USMSTF), adenomas larger than 10mm require a three-year follow-up, while those smaller than 10mm only need a ten-year follow-up (7-year difference).[1] For the European Society for Gastrointestinal endoscopy (ESGE), an adenoma smaller than 10mm would result in patients returning to regular non-colonoscopy-based screening.[2] Small inaccuracies in polyp size measurements can lead to significant delays in patient care, risking increased morbidity or mortality. Accurate size estimation is crucial to adhere to recommendations. Unfortunately, no guidelines state clear, evidence-based recommendations for measuring polyp size. The ESGE recommends standardized measurement of polyp size during endoscopy or pathology examination but does not specify a preference or guidelines for sending samples to pathology (pinned vs. not).[2] Documentation of polyp size is essential for informed decision-making regarding their removal, management, and determining surveillance intervals. According to a Dutch study, only half of colonoscopy reports documented polyp size.[3] The CRC screening and surveillance process typically relies on endoscopists visually measuring polyp size. However, this approach is susceptible to significant inter-operator variations caused by cognitive bias. Therefore, it is crucial to improve the accuracy of polyp size measurement during colonoscopy by utilizing reliable, feasible, and convenient technology.

2. Methods

We conducted a thorough review by searching EMBASE, MEDLINE, and PubMed databases, including adult human studies published in English from inception to 2023. We utilized a sensitive search strategy that involved combining controlled vocabulary and free text terms related to (1) colorectal polyps (neoplasia, carcinoma, tumor) and (2) size measurement. Additionally, we manually searched the references of the identified articles.

3. Clinical Relevance of Polyp Size

3.1 Presence of Advanced Neoplastic Features According to Polyp Size

Most polyps identified during colonoscopy are diminutive and carry low risk of containing or developing advanced histology or cancer.[4-7] A study involving a large cohort of adenomatous polyps revealed that polyps <10mm had <0.005% incidence of advanced histology and cancer.[8]

Although polyps exhibit irregular growth patterns, >40% of polyps tend to grow larger over time.[9, 10] Male gender, black ethnicity, proximal location and multiplicity of polyps were found to be associated with a larger growth size.[9] A 14-year prospective study of 10,947 individuals found that there is a significant association between polyp size, age, gender, and the risk of CRC.[11] Adenomas ≥10mm in size, regardless of histology, are therefore classified as advanced adenomas and are associated with a more than 10-fold higher likelihood of advanced histology and high-grade dysplasia compared to polyps <10mm. [6, 12-15] A meta-analysis of four studies including 20,562 screening subjects revealed that the prevalence of advanced neoplasia increased with larger polyp size, ranging from 0.9% in diminutive polyps to 73.5% in large polyps.[16]

3.2 Importance of Accurate Polyp Sizing for Surveillance Intervals

Post-colonoscopy surveillance intervals are determined by the number, histology, and size of the detected polyps (**Table 1**). Differentiating between 9mm and 10mm polyps is particularly important due to the significant difference in surveillance recommendations according to the latest USMSTF and ESGE guidelines.[1, 2] While endoscopists may overestimate polyp size and recommend shorter intervals for enhanced protection against interval cancer, non-adherence to guidelines driven by fears of interval cancer can impact cost-effectiveness and accessibility of screening programs without effectively reducing colorectal cancer rates.[17] The negative effect of mis-sizing on inappropriate surveillance recommendations still is unknown , and it may be smaller than other factors like undetected polyps and insufficient knowledge of current recommendations.[18-22] Noteworthy, mismanagement due to mis-sizing is more common for larger polyps.[23, 24] In a retrospective study of 189 adenomas ≥6mm, endoscopic mis-sizing was 71.4%, resulting in inappropriate surveillance recommendations for 22% of mis-sized polyps compared to 11% of accurately-measured polyps.[25] Another multi-endoscopist study, polyp mis-sizing ranged from 14% for the most experienced endoscopists to 50% for the least experienced.

Only 7% of endoscopists accurately measured polyp sizes, leading to over 35% of inappropriate surveillance recommendations.[26] Further research is required to replicate these findings in prospective studies.

3.3 Importance of Accurate Polyp Sizing for Optical Diagnosis

The Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) initiative recommends removing and discarding all diminutive polyps without histopathological examination if high-confidence optical diagnosis agrees with pathology in ≥90% of cases, setting appropriate surveillance intervals.[27] Rectosigmoid hyperplastic diminutive polyps can be left in situ if optical predictions achieve ≥90% negative predictive value for adenomas.[27] This approach is justified by the low likelihood of advanced histology or cancer in the majority of colonoscopy-detected diminutive polyps.[4-7] These strategies minimize histopathology exams and allow immediate surveillance interval determination.[28]

A recent study showed that limiting optical diagnosis to 1-3mm polyps increases its feasibility and acceptance among gastroenterologists.[29] Moreover, recent research showed that pathology lacks reliability for determining histology of 1-3mm polyps, while expert endoscopists' high-confidence optical diagnoses align with artificial intelligence predictions but not pathology results.[30-34] A 15-29% discrepancy between optical diagnosis and pathology for 1-3mm polyps indicates the potential of optical diagnosis as an alternative to histopathology.[35, 36] Therefore, accurate polyp size measurement improves cost-effectiveness and reliability of colonoscopy-based screening by integrating optical diagnosis, thereby preventing misclassifications at the 3 and 5mm thresholds.

3.4 Importance of Accurate Polyp Sizing for Choosing Polypectomy Technique

Incomplete resection of neoplastic polyps is a significant risk factor for interval cancer.[37] A recent meta-analysis concluded that 14% of polyps 1-20mm are incompletely resected.[38] Accurate polyp sizing, especially at the 3mm threshold prevents the use of suboptimal polypectomy tools, reducing adverse events, recurrence, and post-colonoscopy CRC. USMSTF guidelines recommend forceps or snare removal for polyps ≥2mm[39, 40]. However, snaring is the preferred method for

removing 1-5mm polyps due to significantly lower rates of incomplete resections compared to forceps (4.4% vs. 9.9%).[38]

4. Methods for Measuring Polyp Size During Colonoscopies

4.1 Factors Associated with Mis-Sizing

Endoscopists commonly visually estimate polyp size without additional instruments, but these estimates are frequently inaccurate, with evidence indicating both underestimation[41-43] and overestimation of the actual size.[44, 45] Interobserver variability in visual size measurements is influenced by various factors.[24] There is a positive correlation between interobserver variability and an increase in polyp size beyond 5mm, regardless of the indication.[24] A large-scale study found that patient's older age and surveillance indication (vs. screening) were associated with overestimating size.[24] Furthermore, experience and training have the potential to improve size estimation accuracy.[42, 46] Although one study showed that endoscopists uniformly underestimated polyp size regardless of their experience level[43], other studies showed that the frequency of mis-sizing is higher among endoscopists with lower experience, leading to a higher rate of mismanagement.[25, 26] The study conducted by Buij et al. demonstrated that measurements of large polyps taken during a second colonoscopy, where EMR or ESD procedures were performed, correlated better with pathology-based sizing compared to measurements taken visually during the index colonoscopy.[47] This improved correlation was attributed to the higher experience of the endoscopists involved in the second colonoscopy and the utilization of measuring tools. These findings highlight the importance of experience and the use of appropriate techniques in accurately measuring polyp size during colonoscopy procedures. The accuracy of polyp size measurement can vary depending on the endoscopist's gender, with studies reporting conflicting results regarding the tendency for mis-sizing between males and females.[24, 48] Polyp morphology also affects size measurement accuracy, with non-pedunculated and sessile polyps more prone to mis-sizing.[25, 48]

Terminal digit preference bias contributes to polyp mis-sizing. In a retrospective study, the size of 92,124 individual polyps was measured endoscopically, with computed tomographic colonography (CTC) and pathological caliper. Clustering polyp sizes at 5mm intervals showed that this bias could lead to an increased proportion of polyps ≥10 mm in size by 2.4% to 5%. [49]

Consequently, this bias may increase the inappropriate referral rate due to reporting of a "pleasing number".[50] Strategies to mitigate this bias include teaching precise polyp sizing to the millimeter level, photodocumenting all lesions before resection with a closed snare tip or biopsy forceps, or with an open snare of known diameter adjacent to the polyp.

4.2 Visual Estimation of The Polyp Size Assisted by Additional Instruments

In the absence of a ground truth for evaluating polyp size, a standard measurement method must be accurate, reliable, and reproducible, regardless of practice settings and endoscopist skills. Over the last few decades, several measurement instruments have been developed and introduced to endoscopy practice, but none have been routinely utilized. If a polypectomy is planned during a colonoscopy, polyp size is often subjectively estimated by placing a biopsy forceps or snare tip adjacent to the polyp as a reference. Otherwise, endoscopists rely on visual estimation of polyp size. Irregular polyp morphology, fragile or bleeding polyp surface, challenges in precise snare placement, the polyp's location on the screen (whether central or peripheral), and endoscopists' terminal digit preference can contribute to polyp mis-sizing when utilizing an additional instrument.[24, 26, 47-49, 51-54] There are three types of single-use measurement tools: non-calibrated, calibrated, and automatic measurement tools.

4.2.1 Non-calibrated measurement tools

4.2.1.1 Biopsy Forceps or snare

Biopsy forceps or snare are valuable measurement tools, especially when targeting small sessile polyps, compared to semi/pedunculated polyps that pose greater in vivo measurement challenges due to their unrestricted movement around the stalk. Chapuis et al. were the first to prove that open biopsy forceps underestimated polyp size compared to pathological measurement.[55] Endoscopists accurately measured only 6% of polyps, with significant underestimation observed for almost all large polyps. However, this study included only rectosigmoid polyps and could not be generalized to other colon segments. In contrast, Morales et al. showed that biopsy forceps are likely to overestimate size by an average of 1.6 mm disregarding endoscopists' experience level.[44] Nonetheless, biopsy forceps can provide an approximately 10% more accurate measurement of polyp size compared to visual estimation

irrespective of the endoscopists' experience, as demonstrated in a Korean multi-endoscopist study (84% vs. 64%).[56]

Biopsy forceps is insufficient in accurately estimating the size of larger polyps due to the maximum diameter of 8-9mm. This can result in incorrect assignment of surveillance intervals and inappropriate selection of polypectomy techniques.[44] The biopsy forceps or snare may not completely open upon exiting the endoscope channel, or align properly with the largest diameter of the polyp. Also, the positioning angle of the forceps or snare on the polyp and the distance between the endoscope tip and the polyp may cause optical misjudgment. Additionally, wide-angle lenses can distort the visual field, compressing peripheral objects and causing underestimation of their size, particularly with larger polyps, known as "barrel distortion." Even when using forceps or snare as a size guide, the measurement of large polyps can be underestimated due to non-uniform distortion across the endoscopic field. Although computer processing systems have been developed to improve forceps/snare size estimation with wide-angle lenses, their practical implementation remains limited.[57, 58]

Furthermore, limited polyp visibility, including obstruction by feces, mucus, or liquid, or when a portion of the polyp is hidden behind a fold, can lead to measurement inaccuracy. Restricted maneuverability of biopsy forceps or snare, especially in the curved sigmoid colon, can cause colonoscope deviation and hinder visibility of the target polyp. Moreover, lack of expertise in using a snare for removing larger polyps and encircling their head rather than targeting their base would lead to inaccurate measurement, particularly for larger sessile polyps with unclear borders. The presence of multiple polyps also complicates the use of a forceps or snare due to increased procedural time and costs.

4.2.2 Calibrated measurement tools

4.2.2.1 Linear Probes

Biopsy forceps and snare can be complemented with linear markings to create linear probes, providing a more accurate size measurement.[59, 60] Gopalswamy et al. compared the accuracy of biopsy forceps size measurement with visual estimation, linear probe, and pathology caliper on post-excision specimens as the gold standard.[60] Biopsy forceps had the largest difference from the gold standard, followed by visual and linear probe methods (12.3%, 3.4%, 6.4%, respectively).

Visual estimation had the highest sensitivity (80%), followed by open biopsy forceps and linear probe (75% for both), and pathologic caliper (55%). All methods had high specificity in size measurements (98% for visual estimation and 93% for other methods).

A disposable graduated biopsy forceps (DGBF), marked at 1mm intervals at its 3cm ending, provides an alternative method for measuring polyp size. However, endoscopists tend to underestimate polyps <1cm and overestimate larger ones compared to post-polypectomy measurements.[61] DGBF's accuracy decreased as polyp size increased (86.7% for <1cm, 66.7% for 1-2cm, 57.1% for >2cm), with visual estimations showing even lower accuracy. Another study confirmed the higher accuracy of DGBF (77.6%) compared to visual estimation (19.0%), showing no significant difference between estimated and actual sizes after polyp excision, while visual estimation tended to result in overestimation.[23] Although DGBF improves measurement accuracy compared to visual estimation, subjectivity and high costs remain significant drawbacks.

A structured light laser probe for one-shot size measurement of polyps was developed by Visentini-Scarzanella et al.[62] It demonstrated comparable accuracy to reference forceps and ruled snare, and outperformed visual assessment using an exploratory porcine stomach. The probe's advantage was its non-occlusive nature, allowing uninterrupted channel usage but the drawbacks included a complex and time-consuming lens cleaning process limited its practical adoption.

A ruler snare can replace biopsy forceps to estimate polyp size, reducing insertions and estimation time when a polypectomy is planned. One study using a graduated injection needles and snares with color-coded markings at 5mm intervals to a maximum of 30mm at the distal sheath compared visual, biopsy forceps, and graduated snare measurements to the actual size measured with a vernier caliper.[45] However, graduated snare showed a higher accuracy (87.5%) for measuring large polyps compared to visual (46.6%) and forceps (58.3%) estimations.

The recently-developped Napoleon Endoscopic Measuring Device (Micro-Tech Endoscopic) offers a catheter-based tool with a 15mm and 30mm ruler. It is calibrated at 1mm intervals with demarcations every 5mm, and can be inserted through the endoscope forceps channel during colonoscopy. A pilot feasibility study demonstrated that this endoscopic ruler could enhance the accuracy of real-time polyp measurement.[63] However, it has not been approved by Health Canada yet.

The limitations of conventional biopsy forceps or snares also apply to graduated biopsy forceps or snares. The use of linear probes requires repeated insertion and removal from the forceps channel for each measurement, which leads to dissatisfaction among endoscopists due to time constraints and cost inefficiencies. Therefore, the systematic use of linear probes in colonoscopy practice is rare.

4.2.2.2 Calibrated Hoods or External Grid on The Endoscopy Monitor

A calibrated hood was developed to address the limitations of linear probes in cap-assisted colonoscopy. [64] It can be easily attached to the endoscope's tip and offers three measurement methods: "Frontal," "Mounted," and "Side" (for sessile polyps). However, it tends to underestimate polyp size compared to immediate post-polypectomy ruler measurements (6.06±1.23mm vs. 5.48±1.31mm).[64]

In a study comparing the calibrated hood to visual assessments, the calibrated hood yielded smaller mean estimated sizes (5.94±1.73 vs. 6.57±2.15).[65] Accuracy in measuring polyp size was overall low regardless of the endoscopist's experience level, with trainees tending to overestimate sizes more than experienced endoscopists. Compared to the linear probe, the calibrated hood offers easier positioning by placing it beside or on the polyp. However, it has a measurement limit of 8mm and requires sufficient skills to be used only during cap-assisted colonoscopy.

The gCAP method uses an external grid applied on the monitor. In a randomized study, gCAP showed higher accuracy and lower discrepancy rates particularly for polyps ≥5mm.[66] However, its practical implementation is limited by the need for a printed grid on transparent vinyl paper within the colonoscopic cap's inner circle and its inability to measure polyps ≥11mm in size due to cap limited diameter.

4.2.3 Automatic tools

4.2.3.1 Artificial Intelligence-Assisted Measurement of Polyp Size

Recent research aims to improve size measurements using machine learning and AI. Computerized models eliminate the need for additional equipment inserted and removed in the

colonoscope channel, but are limited to the latest endoscope generations, posing affordability challenges. Real-time testing under suboptimal bowel preparation or anatomical variations that impede visualization remains unexplored.

Seven studies have explored the use of computer-based models for estimating polyp size. In one study, a modified W-Net convolutional neural networks (CNN) model was developed and tested with retinal image datasets.[67] This model outperformed eight endoscopists estimated polyp sizes visually and with forceps, demonstrating lower interobserver variability and higher accuracy across polyp sizes when tested with still images captured during real-time forceps measurements. However, this model has the disadvantage of the reliance on retinal vascular structure, which differs from the colon's structure rendering it unsuitable for patients with distorted or faint vascular architecture like those with inflammatory bowel disease. Another study utilized a CNN model in real-time colonoscopy and achieved high accuracy levels for categorizing polyps into size groups (~97% for three main size categories).[68] A semi-automatic method and a deep learning model were also employed to estimate polyp size by extending a manual delineation to an entire video sequence using a spatio-temporal characterization of the lesions.[69] However, it showed comparable results to the measurements by endoscopists. Moreover, one study developed a deep learning model that used polyp delineation and detection of landmarks on forceps as the reference for size measurements.[70] Testing on 206 colonoscopy videos with 825 polyps showed that the model had a smaller average difference in size estimation with forceps (0.52mm) compared to visual estimation (1.40mm), suggesting a modest improvement in overcoming underestimation of polyp size by endoscopists. Recently, a computer-aided polyp measurement (CAPME) system was validated using images from 33 colonoscopy videos.[71] Multiple images of 78 detected polyps were measured by two endoscopists, either as individual polyp images or with a biopsy forceps as reference. CAPME showed a strong correlation with both visually-measured and forceps-assisted measurements, demonstrating significantly higher accuracy compared to unassisted measurements by the endoscopists (87.2% vs. 71.8%). Furthermore, the Computer-Aided Sizing AI system (CAPs; Argus–EndoSoft–New York) and Poseidon are two AI-based systems that are recently introduced. CAPs-Argus was validated for both polyp detection and sizing using artificial polyps placed in a colon phantom measured with a caliper as the reference.[72] Argus showed a significantly higher accuracy (96%) compared to expert gastroenterologists (75%), leading to improved surveillance recommendations. Poseidon also achieved a median percentage

error of 7.7% during live colonoscopies, which was significantly lower than median percentage error of 22.1% for visual estimations.[73]

Overall, these computer-based models, including Poseidon, show promise in accurately sizing colorectal polyps and have the potential to enhance clinical practice pending further validation and testing.

4.2.3.2 Virtual Scale Endoscope (VSE, Scale-Eye)

Pending validation of AI systems, a virtual scale function for endoscope, called scale-eye (Fujifilm, Japan) has been introduced as a potential push-button tool for real-time colonoscopy, providing a virtual scale overlay on polyps during live procedures (**Figure 1**). VSE automatically adjusts the scale length ranging 4-30mm based on the the distance between the endoscope tip and the polyp as soon as the endoscope's image sensor detects the laser spot is emitted diagonally from the endoscope tip.[74] **Table 2** summarizes the current literature evaluating the VSE both ex-vivo and in real-time. Masato et al. conducted the first validation study comparing the accuracy of the VSE with biopsy forceps using phantom images.[74] The VSE measurement error was ≤0.7mm as determined using graph paper. VSE had significantly higher accuracy (5.3±5.5%) compared to biopsy forceps (11.9±9.4%) for polyp size measurement ($P<0.001$). Another prospective comparative study using artificial polyps in a colon phantom used caliper-based size estimation as the reference method.[75] The VSE's size estimation demonstrated significantly superior relative accuracy compared to visual size estimation across all polyp size categories, with a greater difference for diminutive polyps compared to those >20mm (29.8% vs. 16.3%). The VSE outperformed visual estimation in terms of smaller interobserver and intraobserver variations and a tendency towards underestimation and underestimation. However, the generalizability of the results is limited due to the hemispherical shape of polyps and the positioning of polyps in the colon phantom, which facilitated easy visualization by the endoscope. Trainees required more time than experts to estimate polyp size using VSE, but the accuracy of size estimation did not vary based on endoscopists' skill level. Therefore, measurement errors were likely due to difficulties in focusing the laser spot on the left edge of the polyp. This issue is more pronounced in hemispherical-shaped polyps compared to those with flat surfaces, as the convex fish-eye lens in dedicated endoscopes can cause the polyp edges to appear smaller and distorted, leading to inaccurate size assessment.

A recent simulated blinded RCT compared the measurement accuracy of VSE, Napoleon ruler, and biopsy forceps against the actual size of artificial polyps measured with a caliper as the reference.[76] VSE demonstrated significantly higher relative measurement accuracy (82.7%) compared to biopsy forceps (78.9%) and Napoleon ruler (78.4%). Experienced endoscopists and trainees had comparable relative accuracy using the three measurement tools. However, the forceps-based accuracy decreased for all endoscopists regardless of their experience level, particularly among trainees. Misclassifications occurred in polyp size categorization at the 10mm threshold. With the Napoleon ruler, biopsy forceps, and VSE, 25.6%, 25.5%, and 22.5% of polyps ≥10mm were misclassified as <10mm. No polyps <10mm were misclassified as ≥10mm with the Napoleon ruler, while 5.5% and 7.1% of these polyps were misclassified with biopsy forceps and VSE, respectively.

A recent pilot study and a RCT (under review) confirmed the superior relative accuracy of VSE compared to the visual estimation of size in real-time (**Video 1, Figure 2**).[77] VSE also showed the advantage of a significantly lower percentage of incorrectly sized >5mm polyps as 1-5mm compared to visual assessment (13.5% vs. 57.1%; p=0.0005). No difference was observed between VSE and visual assessment for the 10mm cut-off size. Additional studies are currently being conducted to further examine the accuracy and generalizability of VSE size measurements.

5. Consideration for Evaluating Size Measurement Methods

Currently, there is no established "gold standard" for polyp size measurement during colonoscopies. New technologies like AI or laser-based systems offer accurate alternatives. Pathological measurement with a caliper or ruler is traditionally considered the reference standard, unaffected by image distortion or endoscopist preferences.[50] However, pathological estimation lacks reliability as the gold standard without further clinical validation due to significant intra-observer and inter-observer variations among pathologists. Factors such as human error and the impact of formalin fixation on polyp diameter contribute to inaccurate measurements. Formalin can cause specimens to shrink by 8-20% in size.[78] Furthermore, if small colorectal polyp specimens are not pinned prior to fixation, tissue shrinkage can occur, affecting anatomical orientation, resection margin evaluation, and accurate pathological assessments.[60, 78] Recent studies found a significant discordance between endoscopic and pathological size

estimations, resulting in mis-sizing of polyp by endoscopists compared to the reference standard of pathological examination.[26, 48, 79-82] Factors associated with the underestimation of size by a pathological ruler include vascular collapse after severing the polyp from its blood supply, polyp desiccation from cautery, and compression of the polyp during removal with a grasper or through endoscope suction.[42, 44, 60, 81]

Endoscopic size measurement is sometimes the only option when polyps are removed piecemeal or if specimens are damaged during retrieval or pathology processing. Currently, the emerging paradigm of intra-colonoscopy polyp sizing represents the most logical and optimal approach for precise and accurate measurement of polyp size, surpassing the limitations of visual or assisted sizing methods like endoscopic ruler or biopsy forceps. this approach effectively circumvents the inherent limitations and drawbacks associated with other non-calibrated or calibrated measurement techniques, including pathological measurements. One notable tool is VSE, which can be easily applied during the procedure and has demonstrated superior accuracy in measuring polyp size across a wide range, from diminutive to large, without requiring further attempts for using an adjunct measurement tool.

6. Conclusion

In conclusion, accurate polyp measurement is crucial for informed decision-making in polypectomy, malignancy risk assessment, optical diagnosis, and surveillance colonoscopies. However, visual estimation of polyp size is subject to variability among endscopists, especially for larger and non-pedunculated polyps. While various measurement methods are available, their systematic application is often limited by financial, time, or technical constraints in most endoscopy centers. Implementing automated and AI-assisted systems has the potential to improve precision without requiring additional instruments. Further research through rigorous clinical trials is necessary to establish their efficiency and cost-effectiveness. AI-based solutions, either standalone or in combination with laser-based systems, can minimize interobserver variability in polyp sizing. Additionally, AI-guided polyp mapping may guide therapeutic interventions for gastrointestinal neoplasms in the future. The VSE offers seamless integration with high-definition endoscopes and demonstrates superior accuracy compared to visual and assisted estimations. It enhances same-day surveillance decisions and optical polyp diagnosis.

Combining VSE with computer-assisted detection (CADe) and classification (CADx) systems improves the effectiveness of colonoscopy in preventing colorectal cancer.

7. References

1. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2020;158(4):1131-1153 e1135. doi:10.1053/j.gastro.2019.10.026. 32044092.
2. Hassan C, Antonelli G, Dumonceau J-M, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2020. Endoscopy. 2020;52(08):687-700.
3. de Jonge V, Sint Nicolaas J, Cahen DL, et al. Quality evaluation of colonoscopy reporting and colonoscopy performance in daily clinical practice. Gastrointest Endosc. 2012;75(1):98-106. doi:10.1016/j.gie.2011.06.032.
4. Vleugels JLA, Hassan C, Senore C, et al. Diminutive Polyps With Advanced Histologic Features Do Not Increase Risk for Metachronous Advanced Colon Neoplasia. Gastroenterology. 2019;156(3):623-634 e623. doi:10.1053/j.gastro.2018.10.050.
5. Gupta N, Bansal A, Rao D, et al. Prevalence of advanced histological features in diminutive and small colon polyps. Gastrointest Endosc. 2012;75(5):1022-1030. doi:10.1016/j.gie.2012.01.020.
6. Lieberman D, Moravec M, Holub J, Michaels L, Eisen G. Polyp size and advanced histology in patients undergoing colonoscopy screening: implications for CT colonography. Gastroenterology. 2008;135(4):1100-1105. doi:10.1053/j.gastro.2008.06.083. PMC2581902.
7. Rex DK. Making a resect-and-discard strategy work for diminutive colorectal polyps: let's get real. Endoscopy. 2021(EFirst).
8. Ponugoti PL, Cummings OW, Rex DK. Risk of cancer in small and diminutive colorectal polyps. Dig Liver Dis. 2017;49(1):34-37. doi:10.1016/j.dld.2016.06.025.
9. Lowenfels AB, Williams JL, Holub JL, Maisonneuve P, Lieberman DA. Determinants of polyp Size in patients undergoing screening colonoscopy. BMC Gastroenterology. 2011;11(1):101. doi:10.1186/1471-230X-11-101.
10. Hofstad B, Vatn M, Andersen SN, et al. Growth of colorectal polyps: redetection and evaluation of unresected polyps for a period of three years. 1996;39(3):449-456.
11. Halfter K, Bauerfeind L, Schlesinger-Raab A, et al. Colonoscopy and polypectomy: beside age, size of polyps main factor for long-term risk of colorectal cancer in a screening population. Journal of Cancer Research and Clinical Oncology. 2021;147(9):2645-2658. doi:10.1007/s00432-021-03532-7.
12. Brenner H, Hoffmeister M, Stegmaier C, Brenner G, Altenhofen L, Haug U. Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies. Gut. 2007;56(11):1585-1589. doi:10.1136/gut.2007.122739. PMC2095643.
13. Rosch T, Altenhofen L, Kretschmann J, et al. Risk of Malignancy in Adenomas Detected During Screening Colonoscopy. Clin Gastroenterol Hepatol. 2018;16(11):1754-1761. doi:10.1016/j.cgh.2018.05.043.
14. Muto T, Bussey HJR, Morson BC. The evolution of cancer of the colon and rectum. Cancer. 1975;36(6):2251-2270. doi:https://doi.org/10.1002/cncr.2820360944.
15. Pickhardt PJ, Pooler BD, Kim DH, Hassan C, Matkowskyj KA, Halberg RB. The Natural History of Colorectal Polyps: Overview of Predictive Static and Dynamic Features. Gastroenterol Clin North Am. 2018;47(3):515-536. doi:10.1016/j.gtc.2018.04.004. PMC6100796.

16. HASSAN C, PICKHARDT PJ, KIM DH, et al. Systematic review: distribution of advanced neoplasia according to polyp size at screening colonoscopy. 2010;31(2):210-217. doi:https://doi.org/10.1111/j.1365-2036.2009.04160.x.
17. Djinbachian R, Dube AJ, Durand M, et al. Adherence to post-polypectomy surveillance guidelines: a systematic review and meta-analysis. Endoscopy. 2019;51(7):673-683. doi:10.1055/a-0865-2082.
18. Barclay RL, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. N Engl J Med. 2006;355(24):2533-2541. doi:10.1056/NEJMoa055498.
19. Kahi CJ, Li X, Eckert GJ, Rex DKJGe. High colonoscopic prevalence of proximal colon serrated polyps in average-risk men and women. 2012;75(3):515-520.
20. Chen SC, Rex DKJOjotACoG, ACG. Endoscopist can be more powerful than age and male gender in predicting adenoma detection at colonoscopy. 2007;102(4):856-861.
21. Goodwin JS, Singh A, Reddy N, Riall TS, Kuo Y-FJAoim. Overuse of screening colonoscopy in the Medicare population. 2011;171(15):1335-1343.
22. Saini SD, Kim HM, Schoenfeld P. Incidence of advanced adenomas at surveillance colonoscopy in patients with a personal history of colon adenomas: a meta-analysis and systematic review. Gastrointest Endosc. 2006;64(4):614-626. doi:10.1016/j.gie.2006.06.057.
23. Liu P, Zhang X, Lin HP, et al. [Study on accuracy of endoscopic polyp size measurement by disposable graduated biopsy forceps]. Zhonghua Wei Chang Wai Ke Za Zhi. 2013;16(12):1142-1145.
24. Elwir S, Shaukat A, Shaw M, Hughes J, Colton J. Variability in, and factors associated with, sizing of polyps by endoscopists at a large community practice. Endosc Int Open. 2017;5(8):E742-e745. doi:10.1055/s-0043-112246. PMC5546891.
25. Pham T, Bajaj A, Berberi L, Hu C, Taleban S. Mis-sizing of Adenomatous Polyps is Common among Endoscopists and Impacts Colorectal Cancer Screening Recommendations. Clin Endosc. 2018;51(5):485-490. doi:10.5946/ce.2017.183. PMC6182286.
26. Eichenseer PJ, Dhanekula R, Jakate S, Mobarhan S, Melson JE. Endoscopic mis-sizing of polyps changes colorectal cancer surveillance recommendations. Dis Colon Rectum. 2013;56(3):315-321. doi:10.1097/DCR.0b013e31826dd138.
27. 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(3):419-422. doi:10.1016/j.gie.2011.01.023.
28. Taghiakbari M, Pohl H, Djinbachian R, et al. The location-based resect and discard strategy for diminutive colorectal polyps: a prospective clinical study. Endoscopy. 2021. doi:10.1055/a-1546-9169.
29. Taghiakbari M, Pohl H, Djinbachian R, et al. What size cutoff level should be used to implement optical polyp diagnosis? Endoscopy. 2022. doi:10.1055/a-1843-9535.
30. Schachschal G, Sehner S, Choschzick M, et al. Impact of reassessment of colonic hyperplastic polyps by expert GI pathologists. Int J Colorectal Dis. 2016;31(3):675-683. doi:10.1007/s00384-016-2523-8.
31. Vleugels JLA, Hazewinkel Y, Dijkgraaf MGW, et al. Optical diagnosis expanded to small polyps: post-hoc analysis of diagnostic performance in a prospective multicenter study. Endoscopy. 2019;51(3):244-252. doi:10.1055/a-0759-1605.
32. Singh H, Bay D, Ip S, et al. Pathological reassessment of hyperplastic colon polyps in a city-wide pathology practice: implications for polyp surveillance recommendations. Gastrointest Endosc. 2012;76(5):1003-1008. doi:10.1016/j.gie.2012.07.026.

33. Anderson JC, Lisovsky M, Greene MA, Hagen C, Srivastava A. Factors Associated With Classification of Hyperplastic Polyps as Sessile Serrated Adenomas/Polyps on Morphologic Review. J Clin Gastroenterol. 2018;52(6):524-529. doi:10.1097/MCG.0000000000000840.
34. Baldin RKS, Anselmi Júnior RA, Azevedo M, et al. Interobserver variability in histological diagnosis of serrated colorectal polyps. Journal of Coloproctology (Rio de Janeiro). 2015;35:193-197.
35. Ponugoti P, Rastogi A, Kaltenbach T, et al. Disagreement between high confidence endoscopic adenoma prediction and histopathological diagnosis in colonic lesions </= 3 mm in size. Endoscopy. 2019;51(3):221-226. doi:10.1055/a-0831-2348.
36. Shahidi N, Rex DK, Kaltenbach T, Rastogi A, Ghalehjegh SH, Byrne MFJG. Use of Endoscopic Impression, Artificial Intelligence, and Pathologist Interpretation to Resolve Discrepancies Between Endoscopy and Pathology Analyses of Diminutive Colorectal Polyps. Gastroenterology. 2020;158(3):783-785. e781.
37. Robertson DJ, Lieberman DA, Winawer SJ, et al. Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. Gut. 2014;63(6):949-956. doi:10.1136/gutjnl-2012-303796. PMC4383397.
38. Djinbachian R, Iratni R, Durand M, Marques P, von Renteln D. Rates of Incomplete Resection of 1- to 20-mm Colorectal Polyps: A Systematic Review and Meta-Analysis. Gastroenterology. 2020;159(3):904-914 e912. doi:10.1053/j.gastro.2020.05.018.
39. Singh N, Harrison M, Rex DK. A survey of colonoscopic polypectomy practices among clinical gastroenterologists. Gastrointest Endosc. 2004;60(3):414-418. doi:10.1016/s0016-5107(04)01808-5.
40. Kaltenbach T, Anderson JC, Burke CA, et al. Endoscopic Removal of Colorectal Lesions—Recommendations by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2020;158(4):1095-1129. doi:10.1053/j.gastro.2019.12.018.
41. Catalano MF, Van Dam J, Bedford R, Cothren RM, Sivak Jr MVJGe. Preliminary evaluation of the prototype stereoscopic endoscope: precise three-dimensional measurement system. 1993;39(1):23-28.
42. Fennerty MB, Davidson J, Emerson SS, Sampliner RE, Hixson LJ, Garewal HSJAJoG. Are endoscopic measurements of colonic polyps reliable? 1993;88(4).
43. Margulies C, Krevsky B, Catalano MFJGe. How accurate are endoscopic estimates of size? 1994;40(2):174-176.
44. Morales TG, Sampliner RE, Garewal HS, Fennerty MB, Aickin MJGe. The difference in colon polyp size before and after removal. 1996;43(1):25-28.
45. Hyun YS, Han DS, Bae JH, Park HS, Eun CS. Graduated injection needles and snares for polypectomy are useful for measuring colorectal polyp size. Digestive and Liver Disease. 2011;43(5):391-394. doi:https://doi.org/10.1016/j.dld.2010.12.015.
46. Schwartz E, Catalano MF, Krevsky BJGe. Endoscopic estimation of size: improved accuracy by directed teaching. 1995;42(4):292-295.
47. Buijs MM, Steele RJC, Buch N, et al. Reproducibility and accuracy of visual estimation of polyp size in large colorectal polyps. Acta Oncol. 2019;58(sup1):S37-s41. doi:10.1080/0284186x.2019.1588990.
48. Anderson BW, Smyrk TC, Anderson KS, et al. Endoscopic overestimation of colorectal polyp size. Gastrointest Endosc. 2016;83(1):201-208. doi:10.1016/j.gie.2015.06.058.
49. Plumb AA, Nickerson C, Wooldrage K, et al. Terminal digit preference biases polyp size measurements at endoscopy, computed tomographic colonography, and histopathology. Endoscopy. 2016;48(10):899-908. doi:10.1055/s-0042-108727.

50. Vleugels JLA, Dekker E. Does polyp size matter? Endosc Int Open. 2017;5(8):E746-E748. doi:10.1055/s-0043-112853.
51. Sakata S, Klein K, Stevenson ARL, Hewett DG. Measurement Bias of Polyp Size at Colonoscopy. Dis Colon Rectum. 2017;60(9):987-991. doi:10.1097/dcr.0000000000000859.
52. Sakata S, McIvor F, Klein K, Stevenson ARL, Hewett DG. Measurement of polyp size at colonoscopy: a proof-of-concept simulation study to address technology bias. 2018;67(2):206-208. doi:10.1136/gutjnl-2016-312915 %J Gut.
53. Hassan C, Repici A, Rex DK. Addressing bias in polyp size measurement. Endoscopy. 2016;48(10):881-883. doi:10.1055/s-0042-112580.
54. Sakata S, Grove PM, Stevenson AR, Hewett DG. The impact of three-dimensional imaging on polyp detection during colonoscopy: a proof of concept study. Gut. 2016;65(5):730-731. doi:10.1136/gutjnl-2016-311507.
55. Chapuis P, Dent O, Goulston KJDotC, Rectum. Clinical accuracy in the diagnosis of small polyps using the flexible fiberoptic sigmoidoscope. 1982;25(7):669-672.
56. Kim JH, Park SJ, Lee JH, et al. Is forceps more useful than visualization for measurement of colon polyp size? 2016;22(11):3220.
57. Vakil N, Smith W, Bourgeois K, Everbach EC, Knyrim K. Endoscopic measurement of lesion size: Improved accuracy with image processing. Gastrointestinal Endoscopy. 1994;40(2):178-183. doi:https://doi.org/10.1016/S0016-5107(94)70163-6.
58. Sonnenberg A, Giger M, Kern L, et al. How reliable is determination of ulcer size by endoscopy? 1979;2(6201):1322-1324. doi:10.1136/bmj.2.6201.1322 %J British Medical Journal.
59. Hofstad B, Vatn M, Larsen S, Osnes MJSjog. Reliability of in situ measurements of colorectal polyps. 1992;27(1):59-64.
60. Gopalswamy N, Shenoy VN, Choudhry U, et al. Is in vivo measurement of size of polyps during colonoscopy accurate? Gastrointest Endosc. 1997;46(6):497-502. doi:10.1016/s0016-5107(97)70003-8.
61. Jin HY, Leng Q. Use of disposable graduated biopsy forceps improves accuracy of polyp size measurements during endoscopy. World J Gastroenterol. 2015;21(2):623-628. doi:10.3748/wjg.v21.i2.623. PMC4296024.
62. Visentini-Scarzanella M, Kawasaki H, Furukawa R, et al. A structured light laser probe for gastrointestinal polyp size measurement: a preliminary comparative study. Endosc Int Open. 2018;6(5):E602-e609. doi:10.1055/a-0577-2798. PMC5943691.
63. Pochapin MB, Khan A, Rosenberg J, et al. S0520 The Napoleon: A Pilot Feasibility Study of a Small Endoscopic Ruler for Accurate Polyp Measurement. 2020;115:S259. doi:10.14309/01.ajg.0000704128.31399.d5.
64. Kume K, Watanabe T, Yoshikawa I, Harada M. Endoscopic measurement of polyp size using a novel calibrated hood. Gastroenterol Res Pract. 2014;2014:714294. doi:10.1155/2014/714294. PMC4100290.
65. Watanabe T, Kume K, Yoshikawa I, Harada MJIjocd. Usefulness of a novel calibrated hood to determine indications for colon polypectomy: visual estimation of polyp size is not accurate. 2015;30(7):933-938.
66. Han S-K, Kim H, Kim J-w, Kim H-S, Kim S-Y, Park H-J. Usefulness of a Colonoscopy Cap with an External Grid for the Measurement of Small-Sized Colorectal Polyps: A Prospective Randomized Trial. 2021;10(11):2365.
67. Kwak MS, Cha JM, Jeon JW, Yoon JY, Park JW. Artificial intelligence-based measurement outperforms current methods for colorectal polyp size measurement. 2022;n/a(n/a). doi:https://doi.org/10.1111/den.14318.

68. Requa J, Dao T, Ninh A, Karnes W. Can a Convolutional Neural Network Solve the Polyp Size Dilemma? Category Award (Colorectal Cancer Prevention) Presidential Poster Award: 282. 2018;113:S158.
69. Martínez F, Ruano J, Gómez M, Romero E. Estimating the size of polyps during actual endoscopy procedures using a spatio-temporal characterization. Computerized Medical Imaging and Graphics. 2015;43:130-136. doi:https://doi.org/10.1016/j.compmedimag.2015.01.002.
70. Suykens J, Eelbode T, Daenen J, Suetens P, Maes F, Bisschops R. Sa2012 AUTOMATED POLYP SIZE ESTIMATION WITH DEEP LEARNING REDUCES INTEROBSERVER VARIABILITY. Gastrointestinal Endoscopy. 2020;91(6):AB241-AB242. doi:10.1016/j.gie.2020.03.1787.
71. Christophe ALLIMANT, Olivier Rouquette, Sophie LE ROUX, et al. COMPUTER-AIDED POLYP MEASUREMENT OF 78 POLYPS DURING LIVE COLONOSCOPY (CAPME) : A PROSPECTIVE STUDY. United European Gastroenterol J. 2017;5 (Supplement 1).
72. Bechtold ML, Dahip MS, Matteson-Kome A, Michelle L., Puli SR, Nguyen DL. S312 Using Artificial Intelligence for Polyp Size in Colonoscopy: A Phantom Study. 2021;116:S136. doi:10.14309/01.ajg.0000773720.82553.5d.
73. Sudarevic B, Sodmann P, Kafetzis I, et al. Artificial intelligence based polyp size measurement in gastrointestinal endoscopy using the auxiliary water jet as a reference. Endoscopy. 2023. doi:10.1055/a-2077-7398.
74. Masato Y, Yuichi S, Daisuke U, et al. Virtual scale function of gastrointestinal endoscopy for accurate polyp size estimation in real-time: a preliminary study. Journal of Biomedical Optics. 2021;26(9):1-10. doi:10.1117/1.JBO.26.9.096002.
75. Shimoda R, Akutagawa T, Tomonaga M, et al. Estimating colorectal polyp size with a virtual scale endoscope and visual estimation during colonoscopy: Prospective, preliminary comparison of accuracy. Dig Endosc. 2022. doi:10.1111/den.14351.
76. Haumesser C, Zarandi-Nowroozi M, Taghiakbari M, et al. Comparing size measurements of simulated colorectal polyps size and morphology groups when using a virtual scale endoscope or visual size estimation: A blinded randomized controlled trial. Dig Endosc. 2022. doi:10.1111/den.14498.
77. von Renteln D, Djinbachian R, Zarandi-Nowroozi M, Taghiakbari M. Measuring size of smaller colorectal polyps using a virtual scale function during endoscopies. Gut. 2022:gutjnl-2022-328654. doi:10.1136/gutjnl-2022-328654.
78. Tran T, Sundaram CP, Bahler CD, et al. Correcting the Shrinkage Effects of Formalin Fixation and Tissue Processing for Renal Tumors: toward Standardization of Pathological Reporting of Tumor Size. J Cancer. 2015;6(8):759-766. doi:10.7150/jca.12094. PMC4504112.
79. Atalaia-Martins C, Marcos P, Leal C, et al. Variation between Pathological Measurement and Endoscopically Estimated Size of Colonic Polyps. GE Port J Gastroenterol. 2019;26(3):163-168. doi:10.1159/000491611. PMC6528088.
80. Chaptini L, Chaaya A, Depalma F, Hunter K, Peikin S, Laine LJGe. Variation in polyp size estimation among endoscopists and impact on surveillance intervals. 2014;80(4):652-659.
81. Schoen RE, Gerber LD, Margulies CJGe. The pathologic measurement of polyp size is preferable to the endoscopic estimate. 1997;46(6):492-496.
82. Moug SJ, Vernall N, Saldanha J, McGregor JR, Balsitis M, Diament RH. Endoscopists' estimation of size should not determine surveillance of colonic polyps. Colorectal Dis. 2010;12(7):646-650. doi:10.1111/j.1463-1318.2009.01870.x.
83. Djinbachian R, Taghiakbari M, Haumesser C, et al. Comparing size measurement of colorectal polyps using a novel virtual scale endoscope, endoscopic ruler or forceps: A preclinical randomized trial. Endosc Int Open. 2023;11(1):E128-e135. doi:10.1055/a-2005-7548.

Table 1 Key recommendations of the post-colonoscopy surveillance intervals according to the US Multi-Society Task Force on Colorectal Cancer guideline (2022).

Polyp histology	**Polyp size <10 mm**				**Polyp size ≥10 mm**
	Polyp number= 1–2	**Polyp number= 3–4**	**Polyp number= 5–10**	**Polyp number >10***	**Any number of polyps**
Hyperplastic	10 years				3–5 years
Conventional adenomas	7–10 years	3–5 years	3 years	1 year	3 years
Sessile serrated polyps/adenomas	5–10 years	3–5 years	3 years	1 year	3 years

*Patients with <20 hyperplastic polyps <10 mm, should undergo surveillance in 10 years.

Table 2 Summary of literature comparing virtual endoscope scale with visual estimation of polyp size.

Study (year)	**Study design**	**Reference standard used**	**Relative accuracy (95% confidence interval)**			**Mean difference of measurements by each tool against the true measurements (mean; mm (Standard deviation))**		
			VSE	**VA**	**p-value**	**VSE**	**VA**	**p-value**
Masato et al (2021)[74]	Ex-vivo exploratory	Graph paper	5.3 ± 5.5%	Biopsy forceps: 11.9 ± 9.4%,	<0.001	-	-	-
Shomida et al (2022)[75]	Ex-vivo	Colon model LM-107 Simulator Type II (Koken Co., Ltd., Tokyo, Japan)	84.0% (SD=11.9)	62.5% (SD=21.1)	<0.001	[a]Mean normalized difference: -12.5	[a]Mean normalized difference: -34.3	<0.001
Djinbachian et al (2022)[83]	Ex-vivo	Simulated polyps measured by a vernier caliper for the largest size	82.7% (80.8-84.8)	Biopsy forceps: 78.9% (76.2-81.5)	<0.001	1.1 (2.1)	Biopsy forceps: 1.9 (2.9)	<0.001
				Napoleon ruler: 78.4% (76.0-80.8)	<0.001		Napoleon ruler: 2.2 (2.9)	<0.001
Haumesser et al (2022)[76]	Ex-vivo	Simulated polyps measured by a vernier	82.0% (80.1-83.9)	71.7% (68.9-74.5)	<0.001	1.3 (3.2)	2.7 (4.8)	<0.001

		caliper for the largest size						
von Renteln et al (2022)[77]	Clinical pilot	Measurements of fresh specimens retrieved post-polypectomy with a vernier caliper	85.4% (81.62-89.26)	66.8% (61.35-72.21)	<0.001	-0.1	-0.2	<0.001
Taghiakbari et al (2023) (under review)	Randomized controlled trial	Measurements of fresh specimens retrieved post-polypectomy with a vernier caliper	84.0% (95% CI, 81.2%-86.7%)	68.4% (64.4%-72.5%)	<0.001	[a]Normalized mean: -0.03; Mean size: 5.4	[a]Normalized mean: -0.25; Mean size: 5.4	<0.001

A: The normalized mean was defined as follows: 100 * (1- ((estimated polyp size - true polyp size)/true polyp size)). VSE: virtual scale endoscope; VA: visual assessment

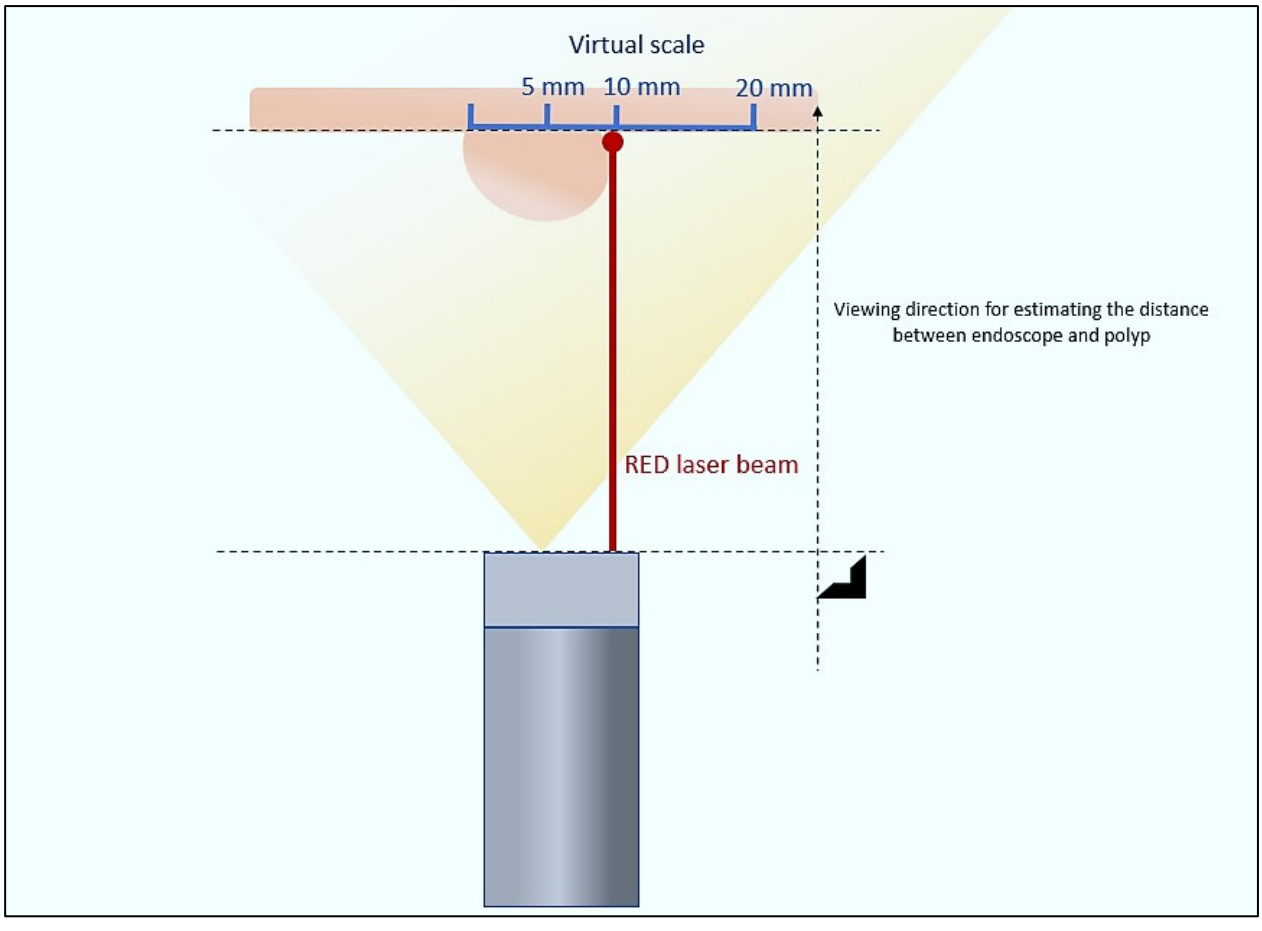


Figure 1 A visual representation of polyp size estimation using the distance between the endoscope tip and the polyp with virtual scale endoscope function.

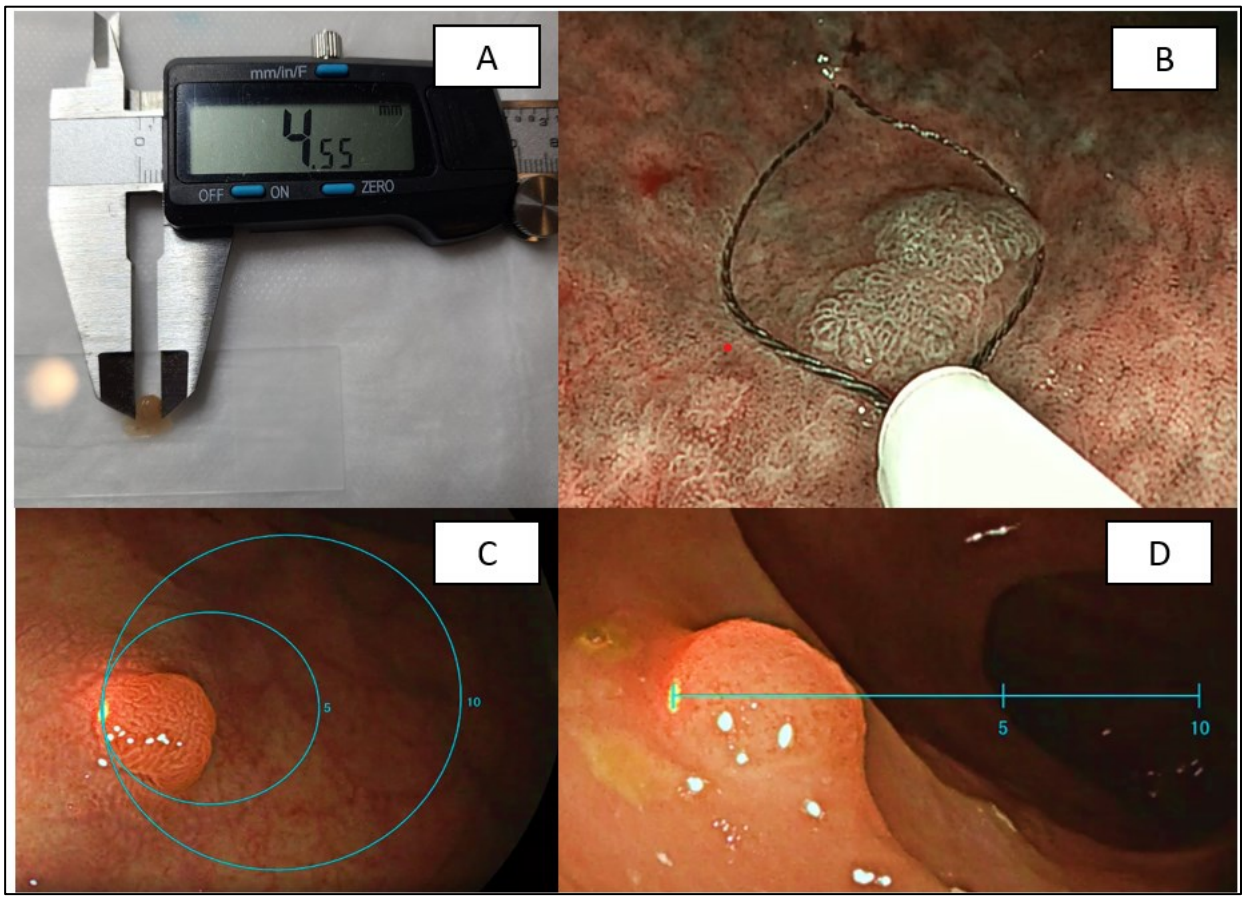


Figure 2 A: Measuring fresh polyp specimens on a glass slide via a vernier caliper immediately after excision and retrieval; B: Measuring polyp size with a snare, this polyp was estimated as 4 mm by the endoscopists and measured as 3.91 mm with caliper; C: Measuring a polyp with virtual scale endoscope using the circular ruler, this polyp was estimated as 3 mm by the endoscopists and measured as 3.75 mm with caliper; D: Measuring a polyp with virtual scale endoscope using the linear ruler, this polyp was estimated as 3 mm by the endoscopists and measured as 3.21 mm with caliper.

Image courtesy: Dr. Daniel von Renteln, 2023.

This video has been inserted as a supplementary material in Appendix 1.

Video 1 Examples of VSE polyp size measurements during colonoscopies.

Chapter 5 – Article 5

Measuring Colorectal Polyp Size Using a Virtual Scale Function During Endoscopies: A Clinical Pilot Study

Daniel von Renteln[1,2], Roupen Djinbachian[1,3], Melissa Zarandi-Nowroozi[1,3], Mahsa Taghiakbari[1,4]

[1]University of Montreal, Montreal, Quebec, Canada; [2]Division of Gastroenterology, University of Montreal Hospital Center (CHUM), Montreal, Quebec, Canada; [3]Division of Internal Medicine, University of Montreal Hospital Center (CHUM), Montreal, Quebec, Canada; [4]University of Montreal Hospital Research Center (CRCHUM), Montreal, Quebec, Canada

1. Message

Polyp size measurements are important for precise polyp risk stratification and follow-up interval decisions. We present the first clinical experience of measuring colorectal polyp size during live colonoscopies using a new endoscope with a laser-based size measurement function (Virtual scale endoscope, VSE). VSE superimposes a virtual linear or circular ruler onto objects in the endoscopist's field of view. When using VSE, we found higher relative accuracy for polyp size measurements (85.4%) compared to visual size estimation (66.8%; $p<0.001$) as compared to polyp size measurement after removal. When looking at the percentage of size measurements that were within 25% of true size (as compared to polyp size measurement after removal) we found that 33.3% for visual polyp size estimation and 86.1% for VSE were within 25% of true size ($p<0.001$).

2. In More Details

Accurate size estimation of colorectal polyps informs the appropriate choice of polypectomy technique and is also crucial for assigning post-colonoscopy surveillance intervals.[1] Furthermore, our understanding of the prevalence of certain polyp pathologies (i.e., high grade or serrated pathology) is in relation to their size.[2] Although accurate polyp size measurement is essential for adequately managing patients, we still rely on the endoscopists' subjective visual estimation of polyp size in routine practice. Current literature shows that subjective visual size estimation of polyp size can be incorrect.[3,4] This can result in erroneous selection of polypectomy techniques and inadequate surveillance intervals. We utilized a novel endoscope (Scale eye, FUJIFILM Co., Tokyo, Japan) with an integrated virtual scale function allowing polyp size measurement during live colonoscopies. The high-definition endoscope emits a red laser beam from its tip diagonally onto the mucosa. The position of the laser beam on the mucosa adaptively changes according to the distance between the object and the tip of the endoscope. This allows superimposition of a linear or circular ruler onto any object in the endoscopist's field of view. The ruler changes in size depending on the distance of the endoscope to the laser point, shrinking with increased distance and growing as the endoscope gets nearer as to always project an accurate size relative to the point of reference. Thus, the virtual scale endoscope (VSE) allows real-time measurement of polyp size using a scale marked at 5, 10, and 20 mm intervals (**Figure 1, video 1**).[5]

We conducted an IRB-approved (CER#21.305) pilot phase (phase 1) of a clinical study (NCT05236790) to evaluate the relative accuracy of VSE for polyp size measurement. Furthermore, we established feasibility to measure polyp size from fresh polypectomy specimens before formalin fixation (**Figure 1**). These reference measurements were compared to visual size estimations and VSE measurements obtained during live colonoscopies. Polyps were initially measured visually before snare polypectomy without using any adjunct instruments or measurement tools as it is common practice during colonoscopies. Then the measurement was repeated using VSE. Endoscopists were instructed to report the largest diameter when obtaining polyp size measurements for each measurement which was documented by a research assistant. Polyps were then resected and removed from the colon to obtain immediate reference size measurements. A "viable specimen" for reference size measurement was defined as any colorectal polyp removed en-bloc with a healthy resection margin around the polyp and retrieved from the colon as intact specimens preserving the entire polyp with a margin of healthy tissue surrounding it (**Figure 1** and **2**). Size measurements for the freshly removed polypectomy specimens was performed using a digital vernier caliper (eSync with 32 feeler gauge measuring with 0.00mm intervals) and a magnification lamp (Veemagi 8X LED lighted) overlooking the evaluation desk. Polyp size measurements were performed for all viable specimens placed on a glass slide and measured directly after polypectomy. When measuring the polyps, the largest diameter was taken as the reference size corresponding to measurements obtained during the colonoscopies. The primary study outcome was the relative accuracy of visual size estimation versus size estimation using VSE. The relative accuracy was calculated as (1- [visual or VSE size-size by caliper]/size by caliper) X100. The secondary outcome was the percentage of measurements that were within 25% of true polyp size. The relative accuracy between visual size estimation and VSE measurements were compared using a paired sample t-test.

Fifty-nine patients (mean age: 63.1 years; 47.5% male) undergoing screening, surveillance, or diagnostic colonoscopies at Centre hospitalier de l'Université de Montréal (CHUM) were included in the pilot study (**Table 1**, **Figure 2**). Colonoscopies were performed by two endoscopists, including one trainee (RD) and one staff gastroenterologist (DvR). In the first 12 patients, we found that when aiming for snare polypectomy with wide resection margins and using a low suction setting, we were able to retrieve 19/44 (43.2%) viable polyp specimens for immediate reference size measurement. In all subsequent patients (n=47), we then obtained for all detected polyps first a visual size estimation and then a VSE polyp size measurement. Polyps were then

resected and retrieved. The fresh specimens were immediately measured on our evaluation desk after removing them from the colon. A total of 72 polyps were detected in these 47 patients and measured visually and then with VSE during the colonoscopy. Polyps that either underwent piece-meal resection, that fractured during the retrieval process, or did not show any healthy resection margin after removal from the colon were excluded (**Figure 2**). After exclusion of these polyps, 36/72 (50%) polyps remained for which visual, VSE, and reference size measurements were available. Polyp mean size measured with the digital caliper (reference size measured after removing the polyp from the colon) was 4.7mm (Standard Deviation (SD) 2.6). Polyp mean size measured during colonoscopies with visual assessment was 4.0mm (SD 2.3) and 4.4 (SD 2.3) when using VSE. Polyp size was significantly closer to reference size when using VSE compared to visual assessment only ($p<0.001$). The relative accuracy of polyp size measurements for visual polyp size estimation was 66.8% (95% confidence interval (CI) 61.35% to 72.21%) and significantly lower compared to the relative accuracy when using VSE (85.4%; 95% CI 81.62% to 89.26%; $p<0.001$). When looking at the percentage of size measurements that were within 25% of true size as measured by the caliper were 33.3% for visual polyp size estimation and 86.1% for VSE ($p<0.001$).

3. Comments

We found significant increase in relative accuracies for measuring polyp size during live colonoscopies when using VSE. Furthermore, we found that when using VSE, the percentage of size measurements that were within 25% of true size is more than doubled and significancy higher. The relative accuracies obtained for visual size estimation and VSE closely resemble those reported in preclinical trials obtained in simulated colon models.[6-8] Similar to these preclinical studies we found in our clinical pilot study that when using VSE the relative accuracy of polyp size measurement is increased from about 60-70% (when using visual size estimation) to about 85%.[6] We chose to obtain reference size measurements from fresh prefixation polyp specimens because tissue specimens shrink between 8-20% in size after fixation in formalin and transport to the pathology lab.[9] In addition, specimen fixation without pinning, which is not typically used for small colorectal polyps, can cause even more tissue shrinkage, problems with anatomical orientation, and difficulty to assess resection margins.[9,10] Furthermore, the timespan of fixation between endoscopic resection and pathology size measurement varies which influences the degree of tissue shrinking.[9,11]

Of course, these results are currently preliminary, based on a small sample size, and require confirmation through the ongoing phase 2 (randomized controlled trial) of our clinical VSE evaluation. Another study limitation is the limited number of large polyps included in our study. There might be an upper size limitation (i.e., non-pedunculated >2cm polyps extending over multiple folds from distal to proximal) where VSE measurement might be more challenging because the obtained reference scale will vary depending on positioning the laser on the proximal or distal portion of the polyp. Validating VSE accuracy for accurate measurement of large flat polyps should follow in a study using ESD for en bloc polyp resection. However, our pilot study allowed us to demonstrate feasibility that polyp reference size can be obtained from fresh polypectomy specimens, and we found such an increase in relative accuracy of size measurement when using VSE for smaller polyps that results became statistically significant in our pilot study. Furthermore, relative accuracy for measuring colorectal polyp size during live colonoscopies closely resembles the results found in preclinical trials using simulated colon models. Validation of these results in randomized controlled trials is ongoing. Finally, improved size measurement accuracy could play an important role in clinically meaningful outcomes in the context of polypectomy or surveillance interval assignment which will require further evaluation in clinical studies.

4. References

1. Kaltenbach T AJ, Burke CA, et al. . Endoscopic removal of colorectal lesions – Recommendations by the US Multi-Society Task Force on Colorectal Cancer. . *Gastroenterology* 2020; **158**: 1095–129.
2. Vleugels JLA, Hassan C, Senore C, et al. Diminutive Polyps With Advanced Histologic Features Do Not Increase Risk for Metachronous Advanced Colon Neoplasia. *Gastroenterology* 2019; **156**(3): 623-34 e3.
3. Pham T, Bajaj A, Berberi L, Hu C, Taleban S. Mis-sizing of Adenomatous Polyps is Common among Endoscopists and Impacts Colorectal Cancer Screening Recommendations. *Clin Endosc* 2018; **51**(5): 485-90.
4. Sakata S, Klein K, Stevenson ARL, Hewett DG. Measurement Bias of Polyp Size at Colonoscopy. *Dis Colon Rectum* 2017; **60**(9): 987-91.
5. Masato Y, Yuichi S, Daisuke U, et al. Virtual scale function of gastrointestinal endoscopy for accurate polyp size estimation in real-time: a preliminary study. *Journal of Biomedical Optics* 2021; **26**(9): 1-10.
6. Shimoda R, Akutagawa T, Tomonaga M, et al. Estimating colorectal polyp size with a virtual scale endoscope and visual estimation during colonoscopy: Prospective, preliminary comparison of accuracy. *Dig Endosc* 2022.
7. Haumesser C, Zarandi-Nowroozi M, Taghiakbari M, et al. A blinded randomized controlled trial comparing endoscopic size measurements of simulated polyps comparing a virtual scale endoscope and visual size estimation. *Digetsive Endoscopy* 2022; **in review**.
8. Djinbachian R, Taghiakbari M, Haumesser C, et al. Comparing size measurement of simulated colorectal polyps when using a novel virtual scale endoscope, endoscopic ruler or forceps: A blinded randomized trial. *Endoscopy Internatonal Open* 2022; **in review**.
9. Tran T, Sundaram CP, Bahler CD, et al. Correcting the Shrinkage Effects of Formalin Fixation and Tissue Processing for Renal Tumors: toward Standardization of Pathological Reporting of Tumor Size. *J Cancer* 2015; **6**(8): 759-66.
10. Gopalswamy N, Shenoy VN, Choudhry U, et al. Is in vivo measurement of size of polyps during colonoscopy accurate? *Gastrointest Endosc* 1997; **46**(6): 497-502.
11. Watanabe M, Kida M, Yamada Y, Saigenji K. Measuring tumor volume with three-dimensional endoscopic ultrasonography: an experimental and clinical study (including video). *Endoscopy* 2004; **36**(11): 976-81.

Table 1 Patient and procedure details and information on polyps for which size measurement was done by VSE, virtual scale endoscope and digital caliper.

Patients' characteristics	**N (%)**
Number of all patients	**43**
Age, years (mean, SD)	63.3 (8.9)
Gender (male)	19 (44.2)
Adequate bowel preparation (BBPS ≥6)	37 (86.0)
Cecal intubation rate	41 (95.3)
Withdrawal time, minute (mean, SD)	17.8 (8.4)
Polyp characteristics	**N (%)**
Number of polyps	**17**
Paris classification	
Ip	1 (5.9)
Is	15 (88.2)
IIc	1 (5.9)
Resection tool	
Cold snare	16 (94.1)
Hot snare	1 (5.9)
Category of size	
1–5 mm	15 (88.2)
6-9 mm	1 (5.9)
10-20 mm	1 (5.9)

SD: standard deviation; VSE: virtual scale endoscope

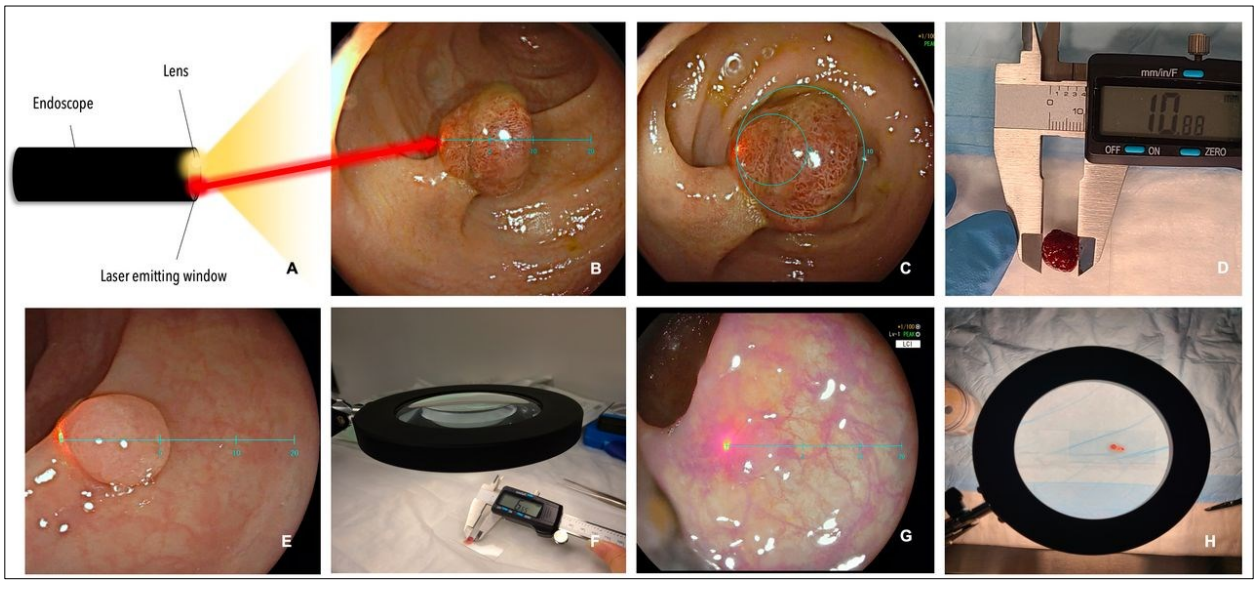
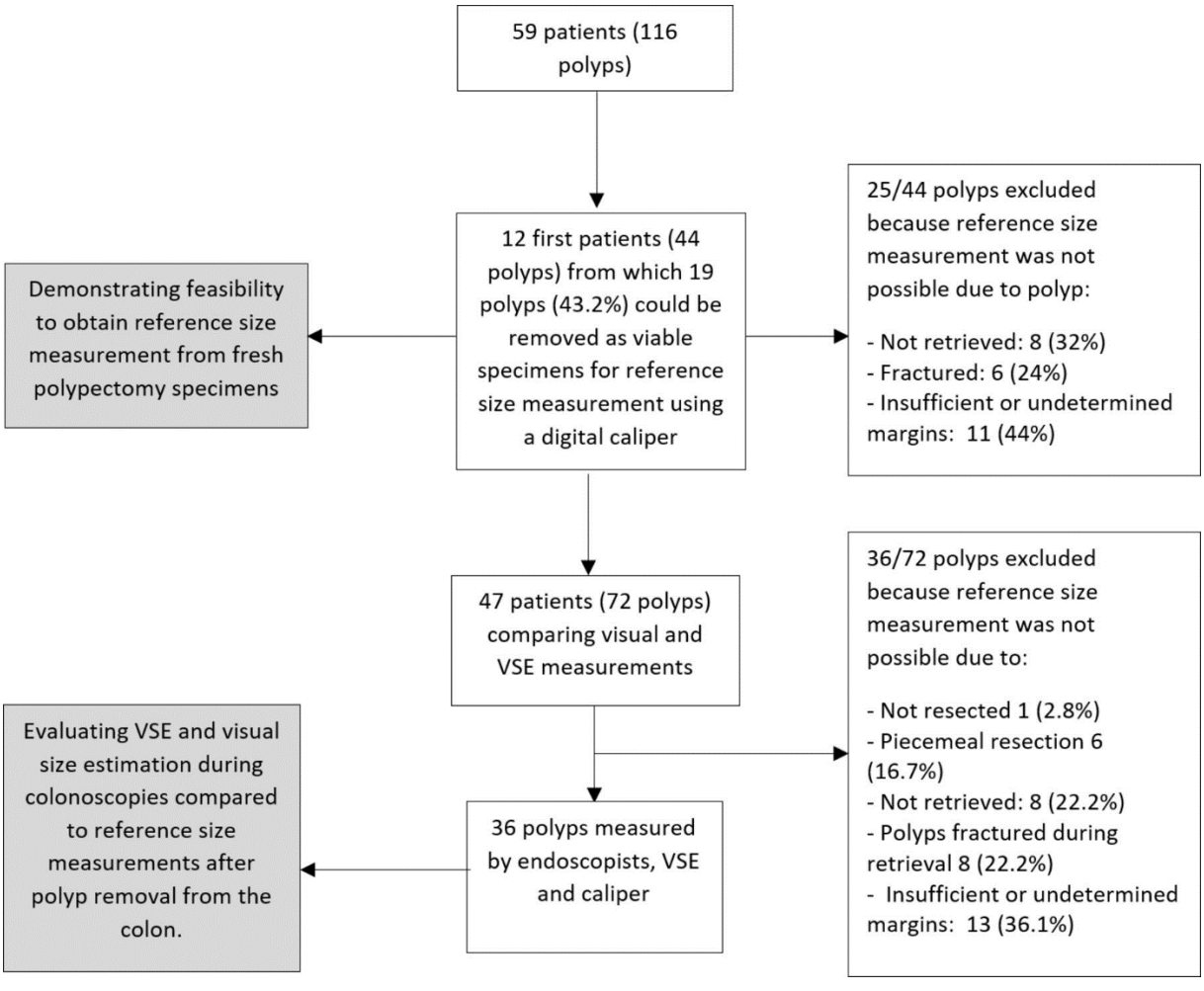


Figure 1 Measuring polyp size during colonoscopies using a virtual scale endoscope (VSE) and obtaining fresh specimen refence size. (A) Illustration of the VSE with the laser emitting window projecting a red laser beam diagonally onto a (B) pedunculated polyp being measured in real-time using the linear scale and (C) the same polyp measured using the VSE circular scale (D) shows the same polyp measured using a digital vernier calliper after retrieval from the colon. (E) A second polyp measured during the colonoscopy and (F) measured on the evaluation table after retrieval from the colon. (G) A third example of a polyp measured during the colonoscopy and (H) showing evaluation after retrieval under the magnification glass.



VSE, virtual scale endoscope.

Figure 2 Study flow chart.

This video has been inserted as a supplementary material in Appendix 1.

Video 2 Examples of VSE polyp size measurements during colonoscopies.

SECTION Ⅲ

Chapter 6: Artificial Intelligence-assisted Colonoscopy: A Review of Current State of Practice and Research

Chapter 7: Automated Detection of Anatomical Landmarks During Colonoscopy Using a Deep Learning Model

Chapter 6 – Article 6

Artificial Intelligence-assisted Colonoscopy: A Review of Current State of Practice and Research

Mahsa Taghiakbari[1], Yuichi Mori[2,3], Daniel von Renteln1

[1]Department of Gastroenterology, CRCHUM, Montreal; [2]Clinical Effectiveness Research Group, University of Oslo, Oslo; [3]Digestive Disease Center, Showa University Northern Yokohama Hospital, Yokohama

Abstract

Colonoscopy is an effective screening procedure in colorectal cancer prevention programs; however, colonoscopy practice can vary in terms of lesion detection, classification, and removal. Artificial intelligence (AI)-assisted decision support systems for endoscopy is an area of rapid research and development. The systems promise improved detection, classification, screening, and surveillance for colorectal polyps and cancer. Several recently developed applications for AI-assisted colonoscopy have shown promising results for the detection and classification of colorectal polyps and adenomas. However, their value for real-time application in clinical practice has yet to be determined owing to limitations in the design, validation, and testing of AI models under real-life clinical conditions. Despite these current limitations, ambitious attempts to expand the technology further by developing more complex systems capable of assisting and supporting the endoscopist throughout the entire colonoscopy examination, including polypectomy procedures, are at the concept stage. However, further work is required to address the barriers and challenges of AI integration into broader colonoscopy practice, to navigate the approval process from regulatory organizations and societies, and to support physicians and patients on their journey to accepting the technology by providing strong evidence of its accuracy and safety. This article takes a closer look at the current state of AI integration into the field of colonoscopy and offers suggestions for future research.

Key Words: Colonoscopy; Adenoma; Artificial intelligence; Computational Intelligence.

Core Tip

Artificial intelligence (AI)-assisted decision support systems for endoscopy have shown promising results for the detection and classification of colorectal lesions. However, their integration into clinical practice is currently limited by the lack of design, validation, and testing under real-life clinical conditions. Further work is required to address the challenges of AI integration, to navigate the regulatory approval process, and to support physicians and patients on their journey to accepting the technology by providing strong evidence of accuracy and safety. This article describes the current state of AI integration into colonoscopy practice and offers suggestions for future research.

1. Introduction

Colorectal cancer (CRC) is the fourth most commonly diagnosed and the third most fatal cancer worldwide in 2018[1]. The prevalence costs of cancer care were estimated to be $14.1 billion for colorectal cancer in the US in 2010[2]. Over the past decade, CRC incidence and mortality have declined as a result of the increase in CRC screening and prevention examinations[3]. Colonoscopy is a screening tool with high sensitivity for the detection of precancerous and cancerous lesions, and may contribute to an approximately 80%, and up to 60% reduction in CRC incidence and mortality, respectively[4-8]. Colonoscopy prevents CRC by breaking the adenoma-carcinoma sequence through detection and removal of premalignant colorectal polyps[3]. Furthermore, it is a cost-effective procedure that often allows surgery to be avoided in patients with adenomas or CRCs that do not invade deeper than the superficial submucosa[9]. However, the quality of colonoscopy procedures is dependent on the experience of the endoscopists, and on the techniques and technology used[10]. A suboptimal colonoscopy examination can result in interval cancers, which are CRCs that occur after a colonoscopy and before the next surveillance examination, and are usually due to non-detection and/or incomplete resection of premalignant polyps. Recent research has shown that CRC precursor lesions are incompletely resected in about 14% of colonoscopy procedures[11]. Quality indicators have been established to describe and measure the quality of colonoscopy examinations[12], and the use of pre- and intraprocedural quality metrics has been shown to result in both an increase in colonoscopy quality and a standardization of procedures[12,13]. One of the most recognized quality metrics is the adenoma detection rate (ADR), which is the proportion of an endoscopist's patients undergoing screening colonoscopy who have at least one adenoma detected; every 1% increase in the ADR has been shown to result in a 3% decrease in the risk of post-colonoscopy CRC[10].

Over 90% of colorectal polyps are diminutive (≤5 mm) or small (≤10 mm), and most of these polyps are non-neoplastic[10]. Recent advances in image-enhanced endoscopy (IEE; *e.g.,* blue-light imaging, narrow-band imaging (NBI), and i-Scan) have resulted in enhanced visualization of the polyp surface pattern. IEE can be employed for the optical classification of colorectal polyps during colonoscopy, obviating the need for pathology[14,15]. The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee, in its Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) statement, has recommended the optical evaluation of diminutive polyps, adopting a "resect and discard" strategy for all diminutive colorectal polyps,

and a “diagnosis and leave” strategy for diminutive rectosigmoid polyps, if the endoscopist can reach the recommended threshold of ≥90% agreement with histopathology results for surveillance interval assignment and ≥90% negative predictive value (NPV) for diagnosis of adenomatous histology, respectively[14,15]. Optical diagnosis can distinguish between neoplastic and non-neoplastic polyps and therefore deliver clinical and cost benefits by reducing the number of unnecessary histopathology examinations and providing immediate surveillance interval recommendations to patients. However, despite the demonstrated high accuracy of optical diagnosis for diminutive polyps, endoscopists have been reluctant to support its broad implementation because of concerns about incorrect diagnoses, assignment of inappropriate surveillance intervals, and related medicolegal issues[16].

To address the shortcomings in current colonoscopy practice, research has been directed at standardizing colonoscopy procedures among endoscopists through the integration of artificial intelligence (AI) into colonoscopy practice. AI could provide real-time support to physicians by automatically recognizing specific polyp patterns in colonoscopy images and/or videos, as well as suggesting the most probable histology and providing a confidence level for the predicted histology. The use of such technology would help to mitigate the effects of endoscopist experience in optical diagnosis. Computer-assisted, or most recently, AI-assisted colonoscopy diagnostic systems (CAD) for detection (CADe) and classification (CADx) of colorectal polyps are currently the two main areas of research and implementation of AI in clinical practice. AI-assisted colonoscopy improves ADR and allows for reliable, operator-independent pathology prediction of colorectal polyps. However, there is still a substantial communication gap between computer and medical fields, with scientists in these two disciplines divided in terms of background knowledge, available resources, research typology, and awareness of unmet needs in clinical practice. In this review, we summarize the most important aspects of the application of CADe and CADx in routine colonoscopy practice.

2. Development of Computer-assisted Diagnostic Systems

Pairing colonoscopy devices with image-enhanced technology (*i.e.,* white-light endoscopy and chromoendoscopy) has improved the quality of care to patients by increasing the precision of colonoscopy procedures[4]. Recently, research efforts have focused on integrating computational

power and previously collected data to enhance the simultaneous detection and classification of colonoscopy images or videos, and to support endoscopists in their decisions about the presence and/or histology of a polyp.

Machine learning is a subset of AI that allows mathematical methods to develop an algorithm based on given data (*e.g.,* polyp images or videos) to predict the same pattern or a specific task in unseen or unknown data[17]. The final output of these systems (*e.g.,* detection or classification of polyps) is based on pre-defined features or extraction of the most relevant image features (*e.g.,* polyps), which may help in the specification, detection, or classification of a new image. In conventional machine learning (*i.e.,* handcrafted models), the clinically relevant polyp features are manually introduced to the machine learning algorithm by a researcher. In contrast, in the most advanced method of machine learning, which is called deep learning, polyp features, clinically relevant or not, are automatically extracted by the algorithm without prior introduction by a researcher. As a result, the output is based on the capture and summary of complex polyp characteristics, either for detection (*i.e.,* discrimination of polyp from background mucosa) or prediction of histopathology (*i.e.,* neoplastic or non-neoplastic)[17]. Deep learning employs deep neural networks (DNNs), which imitates the complex interconnected neural network in the human brain. These artificial neurons are positioned in several detections and pooling layers, taking weighted data (from the precedent layer), processing it, and passing the output (processed data) to the next layer. Each layer performs as a "step of abstraction"[17,] which forms a hierarchy of common features that grow in complexity throughout the layers (i.e., edge->basic shape->object->class prediction). In other words, each layer would extract useful and relevant features from a given data that would facilitate the classification of the images. When data are presented, the DNN performs the repetitive iterations of a previously chosen model (*i.e.,* support vector machines, random forests, or neural networks) throughout the deeper layers, so-called hierarchical feature learning [17]. For computer-assisted colonoscopy, the development of the AI model is primarily based on supervised data, where data are retrospectively labeled by one or a group of expert endoscopists. For example, in CADx, colonoscopy images or videos will be labeled as neoplastic or non-neoplastic based on the reference standard of pathology results (**Figure 1**), which would have been reviewed and finalized following consensus by several pathologists. In CADe, however, polyp images or videos will be reviewed by experienced endoscopists, and polyp borders will be delineated based on consensus by endoscopists. Ultimately, the output of the AI algorithm will identify the presence of a polyp, or be able to discriminate between a neoplastic

and non-neoplastic polyp (**Figure 2**)[17]. However, there are some shortcomings and barriers to the development and implementation of CAD systems in real-time endoscopy practice, as discussed below.

2.1 Datasets

The data used to develop a CAD system will be divided into three or more datasets: one training dataset to build the AI model, one validation dataset to check the generalizability of the model, and at least one test dataset from another source of data to test the performance of the model[17]. Commonly, training and validation data are derived from the same source (*i.e.,* colonoscopies performed at a single center); however, it is crucial to avoid overlap of data, otherwise, evaluation of the model hyperparameters would be flawed and would lead to "model overfitting." Model overfitting is an error in modeling that occurs when the model is too tightly fitted to the training data and random fluctuations in the training data are learned as concepts by the model. The problem is that the fitted model does not generalize to new data due to its low bias and high variance. Overfitting can be avoided by tight monitoring of the model during the training by constantly evaluating the model performance in the training and validation data[17.]

Researchers should use large and heterogeneous data, including normal and abnormal colonoscopies. A sufficient number of colonoscopy images or video frames would ensure a robust evaluation of model performance. Data should ideally be collected from multiple centers and diverse patients in terms of race, age, sex, and medical issues.

A lack of ground truth data or reliable annotated "big data" for generating effective and high-performance AI models could limit the broad application of CAD systems in clinical settings[18]. This is a challenging goal to achieve as it requires millions of colonoscopy images and videos to be annotated by multiple highly experienced experts to ensure a consensus on ambiguous images. Annotation and data labeling by experts should follow a uniform and standardized protocol, otherwise, the generalizability and performance evaluation of the model will be unreliable.

2.2 Gold Standard Comparison

The absence of a "gold standard" for diagnosing polyp histology would affect the accuracy of CAD performance. Although pathology results are currently regarded as the reference standard, the interobserver agreement among pathologists is not 100%; polyp histology determined by one pathologist might be different from that of another pathologist when reassessing the same specimen slides[19-22]. Therefore, the pathology data used for AI models must be re-evaluated by several pathologists prior to inclusion to ensure agreement on polyp pathology.

2.3 Technical Transparency

The application of CAD in routine practice is a product of an interdisciplinary collaboration between medical and AI researchers. A recent review demonstrated that researchers failed to report the AI model characteristics effectively[23]. Researchers should ensure that they clearly define and report the AI model architecture or hyperparameters, including the number of deep layers and learning rate. The definition and testing of hyperparameters are crucial to the validation process owing to their direct effect on the model's performance; optimal model generalizability in the validation step implies the correct choice of hyperparameters. Researchers should briefly explain the source of data, the process of data selection, and the number of patients, including images/videos frames, normal colonoscopies (*i.e.,* without polyp identification), colonoscopy centers, and participating endoscopists together with their level of expertise[17].

Furthermore, researchers should adopt appropriate techniques to prevent model overfitting. Data leakage may occur when the testing dataset results are used to tune the model parameters instead of using the results derived from the validation dataset. Therefore, the model may overfit toward the unseen data, risking a biased estimate of model performance. The stringent use of high-quality still images instead of videos that contain large variability in colonoscopy images may increase the risk of overfitting.

3. Computer-assisted Polyp Detection System (CADe)

In the context of CAD, although the shift from separate engineering and medical disciplines to combined medical and engineering research has gained momentum over the last decade, pilot studies established the idea of CADe as early as 2003[24,25]. The primary hand-crafted AI models used the pre-described polyp features (*e.g.,* color and/or texture-based features) and annotated colonoscopy videos for the detection of colorectal polyps[25-29]. Other studies used the same idea and developed several AI models that resulted in up to 90% sensitivity[30-32]. However, these studies used small and homogeneous datasets to develop and validate the AI models, raising doubts over the model's optimal performance. The hand-crafted features used to build the model led to suboptimal performance, probably because of impaired feature recognition and description, and a high level of false-positive detection owing to the presence of colonic folds, blood vessels, and feces in the lateral view.

After the invention of DNNs, important polyp features could be automatically recognized. Subsequently, the accuracy and sensitivity of models improved, signaling the great potential for CADe application. Recently, Yamada *et al*[33] developed a CADe system using a supervised DNN, and validated the system using a dataset of 705 still images of 752 lesions and 4135 still images of noncancerous tissue. This system performed well, with a sensitivity and specificity of 97.3% and 99.0%, respectively, and an area under the curve (AUC) of 0.975 in the validation set. Misawa *et al*[34] developed a model based on 546 short colonoscopy videos, comprising 155 polyp-positive and 391 polyp-negative videos. Two experts retrospectively annotated videos for polyp presentation to provide a gold standard for comparison. The model presented sensitivity, specificity, and accuracy of 90.0%, 63.3%, and 76.5%, respectively. The polyp detection rate and false-positive detection rate were 95% and 60%, respectively. Other significant research used a large dataset for training an AI model, which comprised 8641 annotated images from over 2000 colonoscopies[35]. The model generated excellent detection capability, with an AUC of 99% and an accuracy of 96.4%. The performance of this model was also superior to that of experts. The authors tested model performance in 20 colonoscopy videos with a total duration of 5 hours, during which colonoscopists removed 28 polyps. After reviewing the videos by four independent experts, eight additional polyps were identified (36 polyps) without the use of AI assistance and 17 additional polyps were detected with AI assistance (total 45 polyps). The model had a false-positive rate of 7%.

Research with a prospective design and focusing on the evaluation of the real-time performance of CADe is scarce. Wang *et al*[36] conducted a prospective non-blinded clinical trial, which aimed to measure ADR with and without the application of CADe. Using 522 and 536 colonoscopies in the control and intervention arms, respectively, the authors found a statistically significant increase in ADR (29.1% *vs* 20.3%) and an increased number of adenomas per patient (0.53 *vs* 0.31) when CADe was used. The false-positive rate was 7.5% per colonoscopy, and there was no significant difference in the procedure time. CADe could detect a higher number of diminutive adenomas and hyperplastic polyps, which represent a higher risk of unnecessary polypectomies, pathology examinations, and longer procedure times. To date, the generalizability of this system has not been tested in Western clinical settings.

In contrast to the results of the latter study, Klare *et al*[37] prospectively evaluated endoscopist performance using CADe assistance during the real-time colonoscopy procedures of 55 patients. However, the endoscopists only observed the regular monitor, and an independent investigator observed the monitor dedicated to representing the real-time outputs of the CADe system in a separate room, which was blinded from the endoscopists' sight. Therefore, the endoscopists were blinded to the real-time CADe outputs. This system did not increase the precision of polyp detection in real-time practice: in per-patient analysis, the application of CADe resulted in endoscopists achieving a lower ADR (29.1% *vs* 30.9%); in per-polyp analysis, CADe could only detect 55 out of 73 polyps previously detected by endoscopists. **Table 1 and 2** shows the summary of the recent studies evaluating a CADe system.

4. Computer-assisted Polyp Classification System (CADx)

Computer-assisted diagnosis of the histopathology of colorectal polyps has become an area of significant research interest because of its potential to prevent the resection of low-risk polyps and reduce the number of unnecessary histopathology examinations. Many studies have successfully developed and validated CADx models, the use of which would allow the "diagnosis and leave strategy" to be implemented. In a prospective pilot study, in which the data from 128 patients undergoing colonoscopy using NBI were used to test a CADx system (209 polyps detected and removed), three polyp features were used to build the AI model: mean vessel length, vessel circumference, and mean brightness within detected blood vessels[38]. The results

showed that the endoscopists' ability to predict polyp histology was superior to that of CADx, which had a sensitivity of 90% and specificity of 70.2% in differentiating neoplastic from non-neoplastic images compared with histopathology as the gold standard. The system's diagnostic performance was compared with that of endoscopists, who were blinded to the histopathology reference standard. Endoscopists accurately predicted polyp histology with a sensitivity of 93.8% and specificity of 85.7% when there was interobserver agreement. In cases of disagreement between endoscopists, the suggested safe prediction of polyp histology (*i.e.,* classification as neoplastic) produced a sensitivity of 96.9% and specificity of 71.4%. Overall, CADx could predict polyp histology with an approximate sensitivity and specificity of 90% and 70%, respectively; however, the overall correct classification rate was moderate (85.3%). Notably, this AI algorithms was not fully automated; thus, its real-time performance in a clinical setting remains to be determined. Another limitation of this study was the use of data from NBI colonoscopies. Although NBI may assist polyp classification, its use may cast doubt on the generalizability of the model, especially in clinical settings where NBI is not available.

The real-time evaluation of CADx is important if the technology is to be integrated into clinical practice. Some studies have used the real-time decision outputs from support vector machines for building CADx algorithms, with promising results[39-43]. Moreover, Chen *et al*[44] demonstrated that an AI model could accurately predict the histopathology of 284 diminutive polyps, comprising 96 hyperplastic and 188 neoplastic polyps diagnosed using NBI, with 96.3% sensitivity, 78.1% specificity, 91.5% NPV, and 89.6% PPV. This study and the study by Byrne *et al*[45] that used the combination of CADe and CADx systems (described below), are remarkable in that they achieved the threshold NPV of ≥90% recommended by the ASGE PIVI statement, favoring the implementation of the "diagnose and leave" strategy for diminutive rectosigmoid polyps[46]. However, the results of the former study need to be confirmed in a prospective study, ideally in a controlled trial, where the probability of selection bias is less, and the AI model can be compared with a conventional setting (without using AI).

More prospective studies assessing CADx are required to support the integration into clinical practice. The existing prospective studies resulted in a high and favorable diagnostic performance, which provided strong evidence to support the real-time application of CADx[47,48]. In contrast, the AI models developed and tested in a prospective trial by Kuiper *et al*[49] did not show sufficient power for differentiating adenomatous from non-adenomatous lesions. Another

CADx model in a prospective study by Rath *et al*[50] could only produce moderate accuracy, sensitivity, and specificity (84.7%, 81.8%, and 85.2%, respectively), although the NPV was relatively high at 96.1%. This model would therefore allow diminutive rectosigmoid polyps to be diagnosed and left *in situ* without resection. The authors suggested that the model's moderate diagnostic performance could be explained by the low prevalence of neoplastic polyps compared with hyperplastic polyps in their dataset, which might proportionately result in an overestimation of the NPV, and an underestimation of the accuracy and PPV of the model. **Table 3** shows the summary of the recent studies evaluating a CADe system.

5. Combined CADe and CADx Models

The ideal CAD system would support the simultaneous detection and classification of polyps to optimize colonoscopy outcomes and achieve the best level of CRC prevention. A recent study evaluated the real-time application of CADx in combination with CADe[45]. The validated model was tested on a series of 125 diminutive polyps, comprising 51 hyperplastic polyps and 74 adenomas. The combined model could not detect histopathology in 15% of polyps. For the remaining 106 polyps histologically predicted with high confidence, the AI model demonstrated an accuracy of 94%, sensitivity of 98%, specificity of 83%, NPV of 97%, and positive predictive value (PPV) of 90%. In a significant study, Byrne *et al*[51] developed a new platform using three distinct AI CADe and CADx algorithms to provide endoscopists with a full workflow from detection to classification: an NBI light detector, a polyp detector, and an optical biopsy. The NBI light detector runs throughout the colonoscopy procedure to ensure the detection of all colorectal polyps with white light imaging, and the optical biopsy provides an accurate polyp classification using NBI light. The NBI light model resulted in an excellent accuracy of 99.94% when tested in 21,804 unseen colonoscopy video frames. However, the detection mode using white light resulted in a sensitivity of only 79%. The optical biopsy model could accurately classify 97.6% of polyps, which was significantly higher than a previous CADx model tested by the same research team[45], and had a sensitivity of 95.95%, specificity of 91.66%, and NPV of 93.6% for polyp classification.

6. Quality Assessment of Colonoscopy by Computer

Few studies have evaluated an AI-assisted system for the ability to accurately and automatically assess the quality of a colonoscopy procedure, including the identification of critical anatomical landmarks, especially when the endoscopic field is blurry[52,53]. Filip *et al*[53] developed a "Colometer" system that could rate colonoscopy quality based on the percentage of the withdrawal time with adequate visualization. This system could detect the factors associated with optimal real-time visualization of the mucosa, including image clarity, withdrawal velocity, and level of bowel cleanliness. A dataset of expert-annotated images and videos was used to train the AI model. The authors compared the quality rated by this system with that of three independent experts. There was a strong correlation between AI and expert quality ratings (ρ coefficient 0.65, P-value 0.01). In another study, a system comprising two AI algorithms was designed to automatically detect the appendiceal orifice on a colon image or video[54]. The first algorithm was developed to detect the appendiceal orifice on endoscopic images based on the local shape, lighting, and intensity differences from a normal edge direction. The second algorithm was designed to detect the appendiceal orifice in the colonoscopy videos using a frame intensity histogram. The system could detect the orifice in images with an average sensitivity and specificity of 96.86% and 90.47%, respectively, and correctly classified 21 out of 23 colonoscopy videos (accuracy 91.30%).

7. Recommendations for Future Research

Despite potential benefits of AI in colonoscopy, regulatory approval and standardization of AI models are difficult goals to achieve for a number of reasons described below:

7.1 Polyp Morphology

Datasets might underrepresent particular polyp morphologies that are not common findings during colonoscopy. For example, non-polypoid lesions with Paris classification of flat and/or depressed morphology are more likely to harbor advanced histology or malignancy but are not a common finding during colonoscopy[55]. The endoscopic detection of non-polypoid lesions is problematic because of their surface pattern resemblance to normal mucosa[56]. Moreover,

serrated polyps comprise about 30% of colon polyps, with sessile serrated polyp/adenoma (SSA/P) prevalence being less than 10%[57]. It has been proven that SSA/Ps can be responsible for CRC through a serrated (hyperplastic-SSP/A-serrated-CRC) sequence[58]. However, SSA/Ps can hardly be distinguished from normal mucosa or hyperplastic polyps by features of crypt distortion. Research has shown that previously diagnosed hyperplastic polyps might be reclassified as SSAs after pathological reassessment[19-22], particularly for larger (>5 mm) or right-sided polyps, and co-existing adenomas containing advanced histology[19,21,59]. A recent meta-analysis showed that pathological reassessment of resected polyps led to a significant change in diagnosis from hyperplastic to SSA for polyps in the right colon and polyps ≥5 mm (odds ratio 4.401 and 8.336, respectively)[59]. Moreover, there is poor agreement among pathologists in the determination of high-risk polyp features owing to the various approaches used for the preparation of biopsy specimens or level of expertise[19,60]. Therefore, the development of an AI platform capable of detecting and distinguishing subtle adenomatous features from normal mucosa with a high level of accuracy would be a valuable clinical tool.

7.2 Metadata

Most studies have failed to assess the performance and accuracy of AI models according to polyp size, polyp location, bowel preparation score, or withdrawal time[18]. Patients' information including demographic and clinical characteristics (e.g., colonoscopy indication, disease status), procedure-related quality characteristics (i.e., bowel preparation level, withdrawal time), procedure time and room, endoscopists fatigue (i.e., the procedure performed in the morning or afternoon) are the important factors that are linked with the long-term non-endoscopic outcome of interest. In other words, the detection and classification of colorectal polyps are the intermediate outcomes of the colonoscopy but the prevention of interval cancer during the surveillance period, or the evaluation of the effectiveness of medical therapy and the need for surgical treatment in patients with inflammatory bowel diseases are the ultimate goals of the colonoscopy depending on the primary indication of the procedure. As mentioned in Kudo *et al*[61], metadata is a critical component in establishing optimal AI platforms that can perform well in real-world practice with suboptimal conditions. For example, SSA/Ps are mainly located in the right colon, where endoscopic access and complete inspection of the mucosa are challenging[58]. Collecting a high number of colonoscopy videos with a high number of SSA/P polyps and cross-

linking with patient's data would increase the accuracy and effectiveness of the colonoscopy. Future AI models must incorporate the information of the polyp size and location as well as the clinical, pre-procedural, and polyp morphological characteristics rather than focusing on the polyp images and videos alone.

7.3 Prospective Real-Time Studies

The robustness of AI platforms has not been widely estimated in real-time clinical settings through prospective studies. Most studies have been retrospective in design and subject to selection bias. Therefore, the comparison of accuracy between model and endoscopists may falsely deviate in favor of CAD. For example, in CADe, the researcher might exclude unclear colonoscopy or polyp images/videos; a fuzzy or blurred endoscopic view may occur when water or blood obscures the field, or when feces cover the bowel surface preventing a complete examination. There should also be a mixture of polyp-positive and polyp-negative images from abnormal and normal colonoscopies in all training, validation, and test datasets. The development of AI models must be rigorously based on a training dataset that is preferably gathered during real-time colonoscopies. Data should be collected prospectively by both experienced and novice endoscopists to represent the actual state of practice when assessing the model. The elimination of selection bias is most relevant to CADe systems and less so to CADx systems. Studies should be based in several centers to ensure the reproducibility of the results at the testing level. Testing CAD systems in non-academic settings will demonstrate whether the model represents actual real-world practice, where more polyps are missed and/or there is no access to advanced technologies such as NBI. In addition, real-time and multicenter studies may help to clarify the place of AI in the diagnostic process. Prospective studies would provide robust evidence to support the application of CAD and enhance endoscopists' trust in optical polyp classification[62]. Nevertheless, CAD is still an operator-dependent technology as it is the experienced endoscopists who must provide the annotated datasets for the development of the system, and the accuracy of the AI output relies on the endoscopist presenting a clear endoscopic field to the system. Certain challenges such as prolonged procedure times, high positivity rate, and inability to predict the histology in the presence of feces or blood in the visual field should be mitigated to prevent suboptimal diagnosis. Physicians should continue to follow the

recommended procedural measures, including sufficient bowel preparation and photo documentation, to avoid legal and insurance issues.

Researchers should prioritize prospective controlled trials to allow a precise comparison between the settings that use and do not use AI platforms, otherwise, the real benefits of the AI system cannot be determined. Crossover studies, where patients act as their own controls and undergo colonoscopy both with and without AI support would be useful as fewer patients would be needed. In practice, the endoscopist would first detect and classify a polyp before using the AI support system to ensure the accuracy of their classification. This process should be performed in a time-efficient manner as the benefit of AI assistance would be irrelevant if the procedure was significantly prolonged.

7.4 Standardization of Endpoints

All research evaluating the diagnostic accuracy of CAD systems should use standardized research endpoints derived from the latest guidelines. Similar to other diagnostic evaluation studies, sensitivity, specificity, PPV, NPV, and AUC must be reported, as well as confusion matrices and mean average precision for multiclass classifications and intersection over union (IoU), or the DICE coefficient for segmentation (*i.e.,* delineation) in particular situations[63,64]. The use of such a comprehensive set of metrics would provide convincing evidence, reassuring physicians about the reliability of AI tools. For example, ADR must be reported for all research related to the evaluation of CADe systems, as the goal of such systems is to achieve complete detection of all colorectal lesions. Similarly, the NPV of CADx systems must be reported to confirm the ability of CADx to achieve the recommended NPV benchmark of ≥90% according to the PIVI statement[46]. In addition, for surveillance interval assignment, the agreement between AI-based assignment and that of the histopathology reference standard must reach the ≥90% threshold recommended by the PIVI statement[46].

7.5 Transparency of AI Analyses

We should avoid the black-box phenomenon when the decision-making process of the model by the convolutional neural network cannot be deconvoluted due to the complexity of the

process[65,66]. An important aspect of the wide application of AI platforms is the trust that physicians and responsible regulatory officials place in the AI analyses. Research should move toward facilitating extreme transparency in the generation and validation of AI models to avoid hesitancy about their public implementation.

7.6 Safety and Cost-effectiveness

Finally, as well as CADe and CADx systems, a computer-based support system that aids endoscopists in selecting the most appropriate polypectomy procedure is necessary. Current practice involves the use of forceps to remove diminutive polyps, especially for the resection of polyps up to 2 mm[67]; however, the rate of incomplete resection is lower for the removal of polyps ≥3 mm when a snare is used[68]. In addition to providing a suggestion for an appropriate polypectomy device, AI can also help to estimate polyp size, delineate the extent of the lesion and a safe polypectomy margin, and identify post-resection lesion remnants that indicate an incomplete resection and the need for further tissue removal at colonoscopy follow-up. The goal of this system is to provide a complete polypectomy that will reduce the risk of interval cancer, as about 30% of all interval cancers are thought to be caused by incomplete resection of CRC precursors[11,69,70].

In addition to addressing the challenges associated with the development of reliable AI models that can be confidently employed in routine practice with high efficacy, research is needed to assess the cost-effectiveness of these systems related to the reduction in the number of patients diagnosed with interval cancer, reduction in the number of unnecessary pathology evaluations for low-confidence predictions of polyp histology by optical diagnosis, and facilitation of efficient physician-patient communication concerning future clinical arrangements.

Adaption of the newly developed AI-based techniques in routine practice, and the enhancement of endoscopists' trust in the new devices is only possible by a symbiotic relationship between academia and industry. It would facilitate obtaining regulatory approval from health authorities regarding research involving human subjects, constructing large "ground truth" data for developing AI models, and transporting knowledge and technology to ultimately access the market[71]. Several manufacturers have obtained the regulatory approvals to launch and commercialize their AI-based colonoscopy devices around the world (**Table 4**); however, many

of them have not provided a detailed report of their devices' performance. Further research should try to compare the performance of different AI-based systems in real-time settings by conducting prospective controlled trials with multiple intervention arms sing different commercially available AI-based colonoscopy systems. Due to the time- and cost-consuming nature of these studies, an alternative method for accelerating research is to test the "benchmarks" using the publicly available datasets such as the ASU-Mayo colonoscopy video database[29], the CVC-ClinicDB database[28], the Kvasir dataset[72], and the ETIS-Larib Polyp database. Nonetheless, these datasets contain a limited number of colonoscopy videos and images and may not reflect the true performance of an AI-based system.

8. Conclusion

AI research is a rapidly evolving discipline that promises to enhance physicians' performance. AI models have demonstrated the ability to compete with and outperform endoscopists, suggesting that all endoscopists would benefit from becoming familiar with CAD technology and comfortable with the integration of AI-assisted devices in colonoscopy practice. The decision support systems are being offered as reliable tools for the detection and classification of colorectal polyps, with the primary aim of outperforming endoscopists by detecting all CRC precursors; however, the new era of AI platforms has seen attempts to establish considerably more complex systems, in which the detection and classification of polyps are supported. Despite the recent achievements in designing and validating such systems, the current lack of AI-assisted systems that support endoscopists in monitoring colonoscopy quality, and that automatically annotate colonoscopy videos, suggest appropriate polypectomy devices, and indicate the completeness of polypectomy, limits the role of AI in colonoscopy practice. Through the integration of the most recent advances in computer science into colonoscopy practice, it appears possible to improve the quality of diagnosis, treatment, and screening in patients. However, AI platforms are still in their infancy in terms of clinical establishment and require much more exploration and innovation. They must be trusted by all physicians, regulatory organizations responsible for approval for clinical use, and patients. The AI-assisted colonoscopy is highly dependent on the endoscopist, who must attempt to present the clearest possible image or video to the AI model for analysis, and then take account of other concurrent patient factors such as the family history of CRC or the results of previous colonoscopies. The human

qualities of respect and empathy must be apparent when communicating with patients to overcome any mistrust or reservations patients may have toward the new technology. Therefore, at the current stage of AI development, AI models can only "serve as a second observer, or a concurrent observer, but not an independent decision-maker"[73].

9. References

1. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. *Prz Gastroenterol* 2019; **14**(2): 89-103PMC6791134.10.5114/pg.2018.81072.https://www.ncbi.nlm.nih.gov/pubmed/31616522.
2. Yabroff KR, Lund J, Kepka D, Mariotto A. Economic burden of cancer in the United States: estimates, projections, and future research. *Cancer Epidemiol Biomarkers Prev* 2011; **20**(10): 2006-2014PMC3191884.10.1158/1055-9965.EPI-11-0650.https://www.ncbi.nlm.nih.gov/pubmed/21980008
https://cebp.aacrjournals.org/content/cebp/20/10/2006.full.pdf.
3. 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**(8): 687-696PMC3322371.10.1056/NEJMoa1100370.https://www.ncbi.nlm.nih.gov/pubmed/22356322.
4. Rex DK, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, Levin TR, Lieberman D, Robertson DJ. Colorectal Cancer Screening: Recommendations for Physicians and Patients From the U.S. Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2017; **153**(1): 307-323.10.1053/j.gastro.2017.05.013.https://www.ncbi.nlm.nih.gov/pubmed/28600072.
5. Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. *Ann Intern Med* 2011; **154**(1): 22-30.10.7326/0003-4819-154-1-201101040-00004.https://www.ncbi.nlm.nih.gov/pubmed/21200035.
6. Brenner H, Chang-Claude J, Jansen L, Knebel P, Stock C, Hoffmeister M. Reduced risk of colorectal cancer up to 10 years after screening, surveillance, or diagnostic colonoscopy. *Gastroenterology* 2014; **146**(3): 709-717.10.1053/j.gastro.2013.09.001.https://www.ncbi.nlm.nih.gov/pubmed/24012982.
7. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009; **150**(1): 1-8.10.7326/0003-4819-150-1-200901060-00306.https://www.ncbi.nlm.nih.gov/pubmed/19075198.
8. Doubeni CA, Corley DA, Quinn VP, Jensen CD, Zauber AG, Goodman M, Johnson JR, Mehta SJ, Becerra TA, Zhao WK, Schottinger J, Doria-Rose VP, Levin TR, Weiss NS, Fletcher RH. Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study. *Gut* 2018; **67**(2): 291-298PMC5868294.10.1136/gutjnl-2016-312712.https://www.ncbi.nlm.nih.gov/pubmed/27733426
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5868294/pdf/gutjnl-2016-312712.pdf.
9. Bartel MJ, Brahmbhatt BS, Wallace MB. Management of colorectal T1 carcinoma treated by endoscopic resection from the Western perspective. *Dig Endosc* 2016; **28**(3): 330-341.10.1111/den.12598.https://www.ncbi.nlm.nih.gov/pubmed/26718885.
10. Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, Zauber AG, de Boer J, Fireman BH, Schottinger JE, Quinn VP, Ghai NR, Levin TR, Quesenberry CP. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014; **370**(14): 1298-1306PMC4036494.10.1056/NEJMoa1309086.https://www.ncbi.nlm.nih.gov/pubmed/24693890
.
11. Kim KO, Huh KC, Hong SP, Kim WH, Yoon H, Kim SW, Kim YS, Park JH, Lee J, Lee BJ, Park YS. Frequency and Characteristics of Interval Colorectal Cancer in Actual Clinical Practice: A KASID Multicenter Study. *Gut Liver* 2018; **12**(5): 537-543PMC6143441.10.5009/gnl17485.https://www.ncbi.nlm.nih.gov/pubmed/29938454.

12. Anderson JC, Butterly LF. Colonoscopy: quality indicators. *Clin Transl Gastroenterol* 2015; **6**(2): e77PMC4418496.10.1038/ctg.2015.5.https://www.ncbi.nlm.nih.gov/pubmed/25716302.
13. Quirke P, Risio M, Lambert R, von Karsa L, Vieth M. Quality assurance in pathology in colorectal cancer screening and diagnosis-European recommendations. *Virchows Arch* 2011; **458**(1): 1-19PMC3016207.10.1007/s00428-010-0977-6.https://www.ncbi.nlm.nih.gov/pubmed/21061133.
14. Rex DK. Can we do resect and discard with artificial intelligence-assisted colon polyp "optical biopsy?". *Techniques and Innovations in Gastrointestinal Endoscopy* 2020; **22**(2): 52-55.10.1016/j.tgie.2019.150638.https://doi.org/10.1016/j.tgie.2019.150638 https://www.tigejournal.org/article/S1096-2883(19)30077-4/pdf.
15. Committee AT, 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**(3): 502 e501-502 e516.10.1016/j.gie.2014.12.022.https://www.ncbi.nlm.nih.gov/pubmed/25597420.
16. Willems P, Djinbachian R, Ditisheim S, Orkut S, Pohl H, Barkun A, Bouin M, Faulques B, von Renteln D. Uptake and barriers for implementation of the resect and discard strategy: an international survey. *Endosc Int Open* 2020; **8**(5): E684-E692PMC7165012 Quebec Sante" career development award and has received research funding from ERBE, Ventage, Pendopharm and Pentax and is a consultant for Boston Scientific and Pendopharm.10.1055/a-1132-5371.https://www.ncbi.nlm.nih.gov/pubmed/32355888.
17. van der Sommen F, de Groof J, Struyvenberg M, van der Putten J, Boers T, Fockens K, Schoon EJ, Curvers W, de With P, Mori Y, Byrne M, Bergman J. Machine learning in GI endoscopy: practical guidance in how to interpret a novel field. *Gut* 2020; **69**(11): 2035-2045PMC7569393.10.1136/gutjnl-2019-320466.https://www.ncbi.nlm.nih.gov/pubmed/32393540.
18. Ahmad OF, Soares AS, Mazomenos E, Brandao P, Vega R, Seward E, Stoyanov D, Chand M, Lovat LB. Artificial intelligence and computer-aided diagnosis in colonoscopy: current evidence and future directions. *Lancet Gastroenterol Hepatol* 2019; **4**(1): 71-80.10.1016/S2468-1253(18)30282-6.https://www.ncbi.nlm.nih.gov/pubmed/30527583 https://www.sciencedirect.com/science/article/abs/pii/S2468125318302826?via%3Dihub.
19. Schachschal G, Sehner S, Choschzick M, Aust D, Brandl L, Vieth M, Wegscheider K, Baretton GB, Kirchner T, Sauter G, Rosch T. Impact of reassessment of colonic hyperplastic polyps by expert GI pathologists. *Int J Colorectal Dis* 2016; **31**(3): 675-683.10.1007/s00384-016-2523-8.https://www.ncbi.nlm.nih.gov/pubmed/26847619.
20. Vleugels JLA, Hazewinkel Y, Dijkgraaf MGW, Koens L, Fockens P, Dekker E, group Ds. Optical diagnosis expanded to small polyps: post-hoc analysis of diagnostic performance in a prospective multicenter study. *Endoscopy* 2019; **51**(3): 244-252.10.1055/a-0759-1605.https://www.ncbi.nlm.nih.gov/pubmed/30544284 https://www.thieme-connect.com/products/ejournals/abstract/10.1055/a-0759-1605.
21. Anderson JC, Lisovsky M, Greene MA, Hagen C, Srivastava A. Factors Associated With Classification of Hyperplastic Polyps as Sessile Serrated Adenomas/Polyps on Morphologic Review. *J Clin Gastroenterol* 2018; **52**(6): 524-529.10.1097/MCG.0000000000000840.https://www.ncbi.nlm.nih.gov/pubmed/28723863 https://www.ingentaconnect.com/content/wk/jcga/2018/00000052/00000006/art00013;jsessionid=1s82qamthh0cw.x-ic-live-01

https://www.ingentaconnect.com/content/wk/jcga/2018/00000052/00000006/art00013;jsessionid=2mfbifb4c77mh.x-ic-live-01.
22. Baldin RKS, Anselmi Júnior RA, Azevedo M, Sebastião APM, Montemor M, Tullio LF, Soares LFdP, Noronha Ld. Interobserver variability in histological diagnosis of serrated colorectal polyps. *Journal of Coloproctology (Rio de Janeiro)* 2015; **35**: 193-197.
23. Lipton ZC, Steinhardt JJapa. Troubling trends in machine learning scholarship. 2018.
24. Maroulis DE, Iakovidis DK, Karkanis SA, Karras DA. CoLD: a versatile detection system for colorectal lesions in endoscopy video-frames. *Comput Methods Programs Biomed* 2003; **70**(2): 151-166.10.1016/s0169-2607(02)00007-x.https://www.ncbi.nlm.nih.gov/pubmed/12507791.
25. Karkanis SA, Iakovidis DK, Maroulis DE, Karras DA, Tzivras M. Computer-aided tumor detection in endoscopic video using color wavelet features. *IEEE Trans Inf Technol Biomed* 2003; **7**(3): 141-152.10.1109/titb.2003.813794.https://www.ncbi.nlm.nih.gov/pubmed/14518727 https://ieeexplore.ieee.org/document/1229852/.
26. Hwang S, Oh J, Tavanapong W, Wong J, Groen PCd. Polyp Detection in Colonoscopy Video using Elliptical Shape Feature. 2007 IEEE International Conference on Image Processing; 2007 16 Sept.-19 Oct. 2007; 2007. p. II - 465-II - 468.
27. Park SY, Sargent D, Spofford I, Vosburgh KG, Y AR. A colon video analysis framework for polyp detection. *IEEE Trans Biomed Eng* 2012; **59**(5): 1408-1418.10.1109/TBME.2012.2188397.https://www.ncbi.nlm.nih.gov/pubmed/22361654.
28. Bernal J, Sanchez FJ, Fernandez-Esparrach G, Gil D, Rodriguez C, Vilarino F. WM-DOVA maps for accurate polyp highlighting in colonoscopy: Validation vs. saliency maps from physicians. *Comput Med Imaging Graph* 2015; **43**: 99-111.10.1016/j.compmedimag.2015.02.007.https://www.ncbi.nlm.nih.gov/pubmed/25863519.
29. Tajbakhsh N, Gurudu SR, Liang JJItomi. Automated polyp detection in colonoscopy videos using shape and context information. 2015; **35**(2): 630-644, https://ieeexplore.ieee.org/document/7294676/.https://ieeexplore.ieee.org/document/7294676/.
30. Wang Y, Tavanapong W, Wong J, Oh JH, de Groen PC. Polyp-Alert: near real-time feedback during colonoscopy. *Comput Methods Programs Biomed* 2015; **120**(3): 164-179.10.1016/j.cmpb.2015.04.002.https://www.ncbi.nlm.nih.gov/pubmed/25952076.
31. Angermann Q, Bernal J, J, Sánchez-Montes C, Hammami M, Fernández-Esparrach G, Dray X, Romain O, Sanchez J, Histace A. Real-Time Polyp Detection in Colonoscopy Videos. International Journal of Computer-Assisted Radiology and Surgery; 2017 2017-06-20; Heidelberg, Germany: Springer; 2017.
32. k G, c R. Automatic Colorectal Polyp Detection in Colonoscopy Video Frames. *Asian Pac J Cancer Prev* 2016; **17**(11): 4869-4873PMC5454689.10.22034/APJCP.2016.17.11.4869.https://www.ncbi.nlm.nih.gov/pubmed/28030914
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5454689/pdf/APJCP-17-4869.pdf.
33. Yamada M, Saito Y, Imaoka H, Saiko M, Yamada S, Kondo H, Takamaru H, Sakamoto T, Sese J, Kuchiba A, Shibata T, Hamamoto R. Development of a real-time endoscopic image diagnosis support system using deep learning technology in colonoscopy. *Sci Rep* 2019; **9**(1): 14465PMC6783454.10.1038/s41598-019-50567-5.https://www.ncbi.nlm.nih.gov/pubmed/31594962.
34. Misawa M, Kudo SE, Mori Y, Cho T, Kataoka S, Yamauchi A, Ogawa Y, Maeda Y, Takeda K, Ichimasa K, Nakamura H, Yagawa Y, Toyoshima N, Ogata N, Kudo T, Hisayuki T, Hayashi T, Wakamura K, Baba T, Ishida F, Itoh H, Roth H, Oda M, Mori K. Artificial Intelligence-Assisted Polyp

Detection for Colonoscopy: Initial Experience. *Gastroenterology* 2018; **154**(8): 2027-2029 e2023.10.1053/j.gastro.2018.04.003.https://www.ncbi.nlm.nih.gov/pubmed/29653147.
35. Urban G, Tripathi P, Alkayali T, Mittal M, Jalali F, Karnes W, Baldi P. Deep Learning Localizes and Identifies Polyps in Real Time With 96% Accuracy in Screening Colonoscopy. *Gastroenterology* 2018; **155**(4): 1069-1078 e1068PMC6174102.10.1053/j.gastro.2018.06.037.https://www.ncbi.nlm.nih.gov/pubmed/29928897.
36. Wang P, Berzin TM, Glissen Brown JR, Bharadwaj S, Becq A, Xiao X, Liu P, Li L, Song Y, Zhang D, Li Y, Xu G, Tu M, Liu X. Real-time automatic detection system increases colonoscopic polyp and adenoma detection rates: a prospective randomised controlled study. *Gut* 2019; **68**(10): 1813-1819PMC6839720.10.1136/gutjnl-2018-317500.https://www.ncbi.nlm.nih.gov/pubmed/30814121.
37. Klare P, Sander C, Prinzen M, Haller B, Nowack S, Abdelhafez M, Poszler A, Brown H, Wilhelm D, Schmid RM, von Delius S, Wittenberg T. Automated polyp detection in the colorectum: a prospective study (with videos). *Gastrointest Endosc* 2019; **89**(3): 576-582 e571.10.1016/j.gie.2018.09.042.https://www.ncbi.nlm.nih.gov/pubmed/30342029.
38. Tischendorf JJ, Gross S, Winograd R, Hecker H, Auer R, Behrens A, Trautwein C, Aach T, Stehle T. Computer-aided classification of colorectal polyps based on vascular patterns: a pilot study. *Endoscopy* 2010; **42**(3): 203-207.10.1055/s-0029-1243861.https://www.ncbi.nlm.nih.gov/pubmed/20101564.
39. Tamaki T, Yoshimuta J, Kawakami M, Raytchev B, Kaneda K, Yoshida S, Takemura Y, Onji K, Miyaki R, Tanaka S. Computer-aided colorectal tumor classification in NBI endoscopy using local features. *Med Image Anal* 2013; **17**(1): 78-100.10.1016/j.media.2012.08.003.https://www.ncbi.nlm.nih.gov/pubmed/23085199.
40. Hirakawa T, Tamaki T, Raytchev B, Kaneda K, Koide T, Kominami Y, Yoshida S, Tanaka S. SVM-MRF segmentation of colorectal NBI endoscopic images. *Annu Int Conf IEEE Eng Med Biol Soc* 2014; **2014**: 4739-4742.10.1109/EMBC.2014.6944683.https://www.ncbi.nlm.nih.gov/pubmed/25571051 https://ieeexplore.ieee.org/document/6944683/.
41. Hafner M, Tamaki T, Tanaka S, Uhl A, Wimmer G, Yoshida S. Local fractal dimension based approaches for colonic polyp classification. *Med Image Anal* 2015; **26**(1): 92-107.10.1016/j.media.2015.08.007.https://www.ncbi.nlm.nih.gov/pubmed/26385078.
42. Wimmer G, Tamaki T, Tischendorf JJ, Hafner M, Yoshida S, Tanaka S, Uhl A. Directional wavelet based features for colonic polyp classification. *Med Image Anal* 2016; **31**: 16-36.10.1016/j.media.2016.02.001.https://www.ncbi.nlm.nih.gov/pubmed/26948110.
43. Okamoto T, Koide T, Sugi K, Shimizu T, Anh-Tuan H, Tamaki T, Raytchev B, Kaneda K, Kominami Y, Yoshida S, Mieno H, Tanaka S. Image segmentation of pyramid style identifier based on Support Vector Machine for colorectal endoscopic images. *Annu Int Conf IEEE Eng Med Biol Soc* 2015; **2015**: 2997-3000.10.1109/EMBC.2015.7319022.https://www.ncbi.nlm.nih.gov/pubmed/26736922 https://ieeexplore.ieee.org/document/7319022/.
44. Chen PJ, Lin MC, Lai MJ, Lin JC, Lu HH, Tseng VS. Accurate Classification of Diminutive Colorectal Polyps Using Computer-Aided Analysis. *Gastroenterology* 2018; **154**(3): 568-575.10.1053/j.gastro.2017.10.010.https://www.ncbi.nlm.nih.gov/pubmed/29042219.
45. Byrne MF, Chapados N, Soudan F, Oertel C, Linares Perez M, Kelly R, Iqbal N, Chandelier F, Rex DK. 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**(1): 94-100PMC6839831.10.1136/gutjnl-2017-314547.https://www.ncbi.nlm.nih.gov/pubmed/29066576.
46. 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**(3): 419-422.10.1016/j.gie.2011.01.023.https://www.ncbi.nlm.nih.gov/pubmed/21353837.
47. Aihara H, Saito S, Inomata H, Ide D, Tamai N, Ohya TR, Kato T, Amitani S, Tajiri H. Computer-aided diagnosis of neoplastic colorectal lesions using 'real-time' numerical color analysis during autofluorescence endoscopy. *Eur J Gastroenterol Hepatol* 2013; **25**(4): 488-494.10.1097/MEG.0b013e32835c6d9a.https://www.ncbi.nlm.nih.gov/pubmed/23249604.
48. Mori Y, Kudo S-e, Misawa M, Saito Y, Ikematsu H, Hotta K, Ohtsuka K, Urushibara F, Kataoka S, Ogawa YJAoim. Real-time use of artificial intelligence in identification of diminutive polyps during colonoscopy: a prospective study. 2018; **169**(6): 357-366.
49. Kuiper T, Alderlieste YA, Tytgat KM, Vlug MS, Nabuurs JA, Bastiaansen BA, Lowenberg M, Fockens P, Dekker E. Automatic optical diagnosis of small colorectal lesions by laser-induced autofluorescence. *Endoscopy* 2015; **47**(1): 56-62.10.1055/s-0034-1378112.https://www.ncbi.nlm.nih.gov/pubmed/25264763
https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0034-1378112.
50. Rath T, Tontini GE, Vieth M, Nagel A, Neurath MF, Neumann H. In vivo real-time assessment of colorectal polyp histology using an optical biopsy forceps system based on laser-induced fluorescence spectroscopy. *Endoscopy* 2016; **48**(6): 557-562.10.1055/s-0042-102251.https://www.ncbi.nlm.nih.gov/pubmed/27009081
https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0042-102251.
51. Byrne MF, Soudan F, Henkel M, Oertel C, Chapados N, Echagüe FJ, Ghalehjegh SH, Guizard N, Giguère S, MacPhail MEJGE. Mo1679 real-time artificial intelligence “full colonoscopy workflow” for automatic detection followed by optical biopsy of colorectal polyps. 2018; **87**(6): AB475.
52. Stanek SR, Tavanapong W, Wong J, Oh J, Nawarathna RD, Muthukudage J, de Groen PC. SAPPHIRE: a toolkit for building efficient stream programs for medical video analysis. *Comput Methods Programs Biomed* 2013; **112**(3): 407-421.10.1016/j.cmpb.2013.07.028.https://www.ncbi.nlm.nih.gov/pubmed/24001925.
53. Filip D, Gao X, Angulo-Rodriguez L, Mintchev MP, Devlin SM, Rostom A, Rosen W, Andrews CN. Colometer: a real-time quality feedback system for screening colonoscopy. *World J Gastroenterol* 2012; **18**(32): 4270-4277PMC3436041.10.3748/wjg.v18.i32.4270.https://www.ncbi.nlm.nih.gov/pubmed/22969189.
54. Wang Y, Tavanapong W, Wong JS, Oh J, de Groen PC. Detection of quality visualization of appendiceal orifices using local edge cross-section profile features and near pause detection. *IEEE Trans Biomed Eng* 2010; **57**(3): 685-695.10.1109/TBME.2009.2034466.https://www.ncbi.nlm.nih.gov/pubmed/19846366.
55. Tsuda S, Veress B, Toth E, Fork FT. Flat and depressed colorectal tumours in a southern Swedish population: a prospective chromoendoscopic and histopathological study. *Gut* 2002; **51**(4): 550-555PMC1773398.10.1136/gut.51.4.550.https://www.ncbi.nlm.nih.gov/pubmed/12235079
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1773398/pdf/gut05100550.pdf.

56. Fidler JL, Johnson CD, MacCarty RL, Welch TJ, Hara AK, Harmsen WS. Detection of flat lesions in the colon with CT colonography. *Abdom Imaging* 2002; **27**(3): 292-300.10.1007/s00261-001-0171-z.https://www.ncbi.nlm.nih.gov/pubmed/12173360 https://link.springer.com/content/pdf/10.1007/s00261-001-0171-z.pdf.
57. JE IJ, de Wit K, van der Vlugt M, Bastiaansen BA, Fockens P, Dekker E. Prevalence, distribution and risk of sessile serrated adenomas/polyps at a center with a high adenoma detection rate and experienced pathologists. *Endoscopy* 2016; **48**(8): 740-746.10.1055/s-0042-105436.https://www.ncbi.nlm.nih.gov/pubmed/27110696 https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0042-105436.
58. 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**(9): 1315-1329; quiz 1314, 1330PMC3629844.10.1038/ajg.2012.161.https://www.ncbi.nlm.nih.gov/pubmed/22710576.
59. Niv Y. Changing pathological diagnosis from hyperplastic polyp to sessile serrated adenoma: systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2017; **29**(12): 1327-1331.10.1097/MEG.0000000000000994.https://www.ncbi.nlm.nih.gov/pubmed/29049128 https://www.ingentaconnect.com/content/wk/ejghe/2017/00000029/00000012/art00002.
60. West NP, Langman G, Haboubi N, Carey F, Henry J, Morgan M, Sheahan K. Significant polyps and early colorectal cancer: the importance of high-quality standardized histopathology. *Colorectal Dis* 2019; **21 Suppl 1**(S1): 53-56.10.1111/codi.14506.https://www.ncbi.nlm.nih.gov/pubmed/30809908.
61. Kudo SE, Mori Y, Misawa M, Takeda K, Kudo T, Itoh H, Oda M, Mori K. Artificial intelligence and colonoscopy: Current status and future perspectives. *Dig Endosc* 2019; **31**(4): 363-371.10.1111/den.13340.https://www.ncbi.nlm.nih.gov/pubmed/30624835.
62. East JE, Rees CJ. Making optical biopsy a clinical reality in colonoscopy. *Lancet Gastroenterol Hepatol* 2018; **3**(1): 10-12.10.1016/S2468-1253(17)30366-7.https://www.ncbi.nlm.nih.gov/pubmed/29254613 https://www.sciencedirect.com/science/article/abs/pii/S2468125317303667?via%3Dihub.
63. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, Lijmer JG, Moher D, Rennie D, de Vet HC, Kressel HY, Rifai N, Golub RM, Altman DG, Hooft L, Korevaar DA, Cohen JF, Group S. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ* 2015; **351**: h5527PMC4623764.10.1136/bmj.h5527.https://www.ncbi.nlm.nih.gov/pubmed/26511519.
64. Dice LR. Measures of the Amount of Ecologic Association Between Species. *Ecology* 1945; **26**(3): 297-302.10.2307/1932409.https://doi.org/10.2307/1932409 https://esajournals.onlinelibrary.wiley.com/doi/pdfdirect/10.2307/1932409?download=true.
65. Montavon G, Samek W, Müller K-R. Methods for interpreting and understanding deep neural networks. *Digital Signal Processing* 2018; **73**: 1-15.10.1016/j.dsp.2017.10.011.http://www.sciencedirect.com/science/article/pii/S1051200417302385.
66. Japkowicz N, Shah M. Evaluating Learning Algorithms: A Classification Perspective: Cambridge University Press; 2011.
67. Fyock CJ, Draganov PV. Colonoscopic polypectomy and associated techniques. *World J Gastroenterol* 2010; **16**(29): 3630-3637PMC2915422.10.3748/wjg.v16.i29.3630.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2915422/pdf/WJG-16-3630.pdf.

68. Shaukat A, Kaltenbach T, Dominitz JA, Robertson DJ, Anderson JC, Cruise M, Burke CA, Gupta S, Lieberman D, Syngal S, Rex DK. Endoscopic Recognition and Management Strategies for Malignant Colorectal Polyps: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. *Gastrointestinal Endoscopy* 2020; **92**(5): 997-1015.e1011.https://doi.org/10.1016/j.gie.2020.09.039.https://www.sciencedirect.com/science/article/pii/S0016510720348410.
69. Samadder NJ, Curtin K, Tuohy TM, Pappas L, Boucher K, Provenzale D, Rowe KG, Mineau GP, Smith K, Pimentel R, Kirchhoff AC, Burt RW. Characteristics of missed or interval colorectal cancer and patient survival: a population-based study. *Gastroenterology* 2014; **146**(4): 950-960.10.1053/j.gastro.2014.01.013.https://www.ncbi.nlm.nih.gov/pubmed/24417818.
70. Farrar WD, Sawhney MS, Nelson DB, Lederle FA, Bond JH. Colorectal cancers found after a complete colonoscopy. *Clin Gastroenterol Hepatol* 2006; **4**(10): 1259-1264.10.1016/j.cgh.2006.07.012.https://www.ncbi.nlm.nih.gov/pubmed/16996804.
71. Mori Y, Neumann H, Misawa M, Kudo S-e, Bretthauer M. Artificial intelligence in colonoscopy - Now on the market. What's next? 2021; **36**(1): 7-11.https://doi.org/10.1111/jgh.15339.https://onlinelibrary.wiley.com/doi/abs/10.1111/jgh.15339
https://onlinelibrary.wiley.com/doi/10.1111/jgh.15339
https://onlinelibrary.wiley.com/doi/pdfdirect/10.1111/jgh.15339?download=true.
72. Pogorelov K, Randel KR, Griwodz C, Eskeland SL, de Lange T, Johansen D, Spampinato C, Dang-Nguyen D-T, Lux M, Schmidt PT. Kvasir: A multi-class image dataset for computer aided gastrointestinal disease detection. Proceedings of the 8th ACM on Multimedia Systems Conference; 2017; 2017. p. 164-169.
73. Fernandez-Esparrach G, Bernal J, Lopez-Ceron M, Cordova H, Sanchez-Montes C, Rodriguez de Miguel C, Sanchez FJ. Exploring the clinical potential of an automatic colonic polyp detection method based on the creation of energy maps. *Endoscopy* 2016; **48**(9): 837-842.10.1055/s-0042-108434.https://www.ncbi.nlm.nih.gov/pubmed/27285900
https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0042-108434.
74. Wang P, Liu X, Berzin TM, Glissen Brown JR, Liu P, Zhou C, Lei L, Li L, Guo Z, Lei S, Xiong F, Wang H, Song Y, Pan Y, Zhou G. Effect of a deep-learning computer-aided detection system on adenoma detection during colonoscopy (CADe-DB trial): a double-blind randomised study. *The Lancet Gastroenterology & Hepatology* 2020; **5**(4): 343-351.https://doi.org/10.1016/S2468-1253(19)30411-X.https://www.sciencedirect.com/science/article/pii/S246812531930411X
https://www.sciencedirect.com/science/article/abs/pii/S246812531930411X?via%3Dihub.
75. Su JR, Li Z, Shao XJ, Ji CR, Ji R, Zhou RC, Li GC, Liu GQ, He YS, Zuo XL, Li YQ. Impact of a real-time automatic quality control system on colorectal polyp and adenoma detection: a prospective randomized controlled study (with videos). *Gastrointest Endosc* 2020; **91**(2): 415-424.e414.10.1016/j.gie.2019.08.026.
76. Gong D, Wu L, Zhang J, Mu G, Shen L, Liu J, Wang Z, Zhou W, An P, Huang X, Jiang X, Li Y, Wan X, Hu S, Chen Y, Hu X, Xu Y, Zhu X, Li S, Yao L, He X, Chen D, Huang L, Wei X, Wang X, Yu H. Detection of colorectal adenomas with a real-time computer-aided system (ENDOANGEL): a randomised controlled study. *The Lancet Gastroenterology & Hepatology* 2020; **5**(4): 352-361.https://doi.org/10.1016/S2468-1253(19)30413-3.https://www.sciencedirect.com/science/article/pii/S2468125319304133
https://www.sciencedirect.com/science/article/abs/pii/S2468125319304133?via%3Dihub.
77. Liu WN, Zhang YY, Bian XQ, Wang LJ, Yang Q, Zhang XD, Huang J. Study on detection rate of polyps and adenomas in artificial-intelligence-aided colonoscopy. *Saudi J Gastroenterol* 2020;

26(1): 13-19PMC7045775.10.4103/sjg.SJG_377_19.https://www.ncbi.nlm.nih.gov/pubmed/31898644 https://www.saudijgastro.com/article.asp?issn=1319-3767;year=2020;volume=26;issue=1;spage=13;epage=19;aulast=Liu https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7045775/pdf/SJG-26-13.pdf.

78. Luo Y, Zhang Y, Liu M, Lai Y, Liu P, Wang Z, Xing T, Huang Y, Li Y, Li A, Wang Y, Luo X, Liu S, Han Z. Artificial Intelligence-Assisted Colonoscopy for Detection of Colon Polyps: a Prospective, Randomized Cohort Study. *Journal of Gastrointestinal Surgery* 2021; **25**(8): 2011-2018.10.1007/s11605-020-04802-4.https://doi.org/10.1007/s11605-020-04802-4 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8321985/pdf/11605_2020_Article_4802.pdf.

79. Repici A, Badalamenti M, Maselli R, Correale L, Radaelli F, Rondonotti E, Ferrara E, Spadaccini M, Alkandari A, Fugazza A, Anderloni A, Galtieri PA, Pellegatta G, Carrara S, Di Leo M, Craviotto V, Lamonaca L, Lorenzetti R, Andrealli A, Antonelli G, Wallace M, Sharma P, Rosch T, Hassan C. Efficacy of Real-Time Computer-Aided Detection of Colorectal Neoplasia in a Randomized Trial. *Gastroenterology* 2020; **159**(2): 512-520.e517.https://doi.org/10.1053/j.gastro.2020.04.062.https://www.sciencedirect.com/science/article/pii/S0016508520305837.

80. Wang P, Liu P, Glissen Brown JR, Berzin TM, Zhou G, Lei S, Liu X, Li L, Xiao X. Lower Adenoma Miss Rate of Computer-Aided Detection-Assisted Colonoscopy vs Routine White-Light Colonoscopy in a Prospective Tandem Study. *Gastroenterology* 2020; **159**(4): 1252-1261.e1255.10.1053/j.gastro.2020.06.023.

81. Park SY, Sargent D. Colonoscopic polyp detection using convolutional neural networks. SPIE Medical Imaging; 2016; 2016.

82. Yu L, Chen H, Dou Q, Qin J, Heng PAJIjob, informatics h. Integrating online and offline three-dimensional deep learning for automated polyp detection in colonoscopy videos. 2016; **21**(1): 65-75.

83. Billah M, Waheed S, Rahman MMJIjobi. An automatic gastrointestinal polyp detection system in video endoscopy using fusion of color wavelet and convolutional neural network features. 2017; **2017**.

84. Zhang R, Zheng Y, Mak TW, Yu R, Wong SH, Lau JY, Poon CC. Automatic Detection and Classification of Colorectal Polyps by Transferring Low-Level CNN Features From Nonmedical Domain. *IEEE J Biomed Health Inform* 2017; **21**(1): 41-47.10.1109/JBHI.2016.2635662.https://www.ncbi.nlm.nih.gov/pubmed/28114040 https://ieeexplore.ieee.org/document/7769237/.

85. Wang P, Xiao X, Glissen Brown JR, Berzin TM, Tu M, Xiong F, Hu X, Liu P, Song Y, Zhang D, Yang X, Li L, He J, Yi X, Liu J, Liu X. Development and validation of a deep-learning algorithm for the detection of polyps during colonoscopy. *Nature Biomedical Engineering* 2018; **2**(10): 741-748.10.1038/s41551-018-0301-3.https://doi.org/10.1038/s41551-018-0301-3 https://www.nature.com/articles/s41551-018-0301-3.

86. Ozawa T, Ishihara S, Fujishiro M, Kumagai Y, Shichijo S, Tada T. Automated endoscopic detection and classification of colorectal polyps using convolutional neural networks. 2020; **13**: 1756284820910659.10.1177/1756284820910659.https://journals.sagepub.com/doi/abs/10.1177/1756284820910659 https://journals.sagepub.com/doi/pdf/10.1177/1756284820910659.

87. Mori Y, Kudo SE, Wakamura K, Misawa M, Ogawa Y, Kutsukawa M, Kudo T, Hayashi T, Miyachi H, Ishida F, Inoue H. Novel computer-aided diagnostic system for colorectal lesions by using endocytoscopy (with videos). *Gastrointest Endosc* 2015; **81**(3): 621-629.10.1016/j.gie.2014.09.008.

88. Song EM, Park B, Ha CA, Hwang SW, Park SH, Yang DH, Ye BD, Myung SJ, Yang SK, Kim N, Byeon JS. Endoscopic diagnosis and treatment planning for colorectal polyps using a deep-learning model. *Sci Rep* 2020; **10**(1): 30PMC6949236.10.1038/s41598-019-56697-0.https://www.ncbi.nlm.nih.gov/pubmed/31913337.
89. Kudo SE, Misawa M, Mori Y, Hotta K, Ohtsuka K, Ikematsu H, Saito Y, Takeda K, Nakamura H, Ichimasa K, Ishigaki T, Toyoshima N, Kudo T, Hayashi T, Wakamura K, Baba T, Ishida F, Inoue H, Itoh H, Oda M, Mori K. Artificial Intelligence-assisted System Improves Endoscopic Identification of Colorectal Neoplasms. *Clin Gastroenterol Hepatol* 2020; **18**(8): 1874-1881 e1872.10.1016/j.cgh.2019.09.009.https://www.ncbi.nlm.nih.gov/pubmed/31525512.

Table 1 Summary of the randomized controlled trials involving computer-aided detection (CADe) for colonoscopy.

Author	Year	Study design	Study aim	CADe system	Image modality	Number of patients in the CADe group	Number of patients in the control group	Number of polyps (CADe vs control group)	Adenoma detection rate (%) (CADe vs control group)	Polyp detection rate (%) (CADe vs control group)	Number of false-positive (rate (%)) (CADe vs control group)	Withdrawal time (CADe vs control group), min ± SD; minute
Wang et al[36]	2019	Non-blinded prospective randomised controlled study	To investigate whether a high-performance real-time CADe system can increase polyp and adenoma detection rates in the real clinical setting.	The real-time automatic polyp detection system (Shanghai Wision AI Co., Ltd.) based on artificial neural network-SegNet architecture	Real-time Video stream	522	536	767 (498 vs 269)	29.1 vs 20.3; p<0.001; 95% CI=1.21-2.135	45.0 vs 29.1; p<0.001; 95% CI=1.532-2.544	39 vs 0	6.18±1.38 vs 6.07±1.11; p=0.15
Wang et al[74]	2020	Double-blind Prospective	To assess the effectiveness of a CADe system for	The real-time automatic polyp detection system (Shanghai	Real-time Video stream	484	478	809 (501 vs 308)	34.0 vs 28.0; p=0.030; OR=1.36, 95%	52.0 vs 37.0; p <0.0001;	48 in CADe group (control	6.48±1.32 vs 6.37±1.09; p=0.14

		randomised trial	improving detection of colon adenomas and polyps; to analyse the characteristics of polyps missed by endoscopists.	Wision AI Co., Ltd.) based on artificial neural network-SegNet architecture					CI=1.03–1.79	OR=1.86, 95% CI=1.44–2.41	group not reported)	
Su et al[75]	2020	Single-blind Prospective randomised trial	To develop an automatic quality control system; to investigate whether the system could increase the detection of polyps and adenomas in real clinical practice.	Five deep learning convolutional neural networks (DCNNs) based on AlexNet, ZFNet, and YOLO V2	Real-time Video stream	308	315	273 (177 vs 96)	28.9 vs 16.5; p <0.001; OR=2.055, 95%CI=1.397-3.024	38.3 vs 25.4; p=0.00; OR=1.824, 95% CI=1.296-2.569	62 in CADe system (control group not reported)	7.03± 1.01 vs 5.6± 1.26; P <0.001

Gong et al[76]	2020	Single-blind Prospective randomised trial	To evaluate whether the CADe system could improve polyp yield during colonoscopy.	ENDOANGEL based on the deep neural networks and perceptual hash algorithms	Real-time Video stream	355	349	302 (178 vs 124)	16 vs 8; p=0.001; OR=2.30, 95% CI=1.40-3·77	47 vs 34; p=0.0016; OR=1.69, 95% CI=1.22-2.34	For endoscope being inside=0.8; For identification of the caecum=2; for prediction of slipping=0	6.38±2·48 vs 4.76±254; p <0.0001
Liu et al[77]	2020	Double-blind Prospective randomised trial	To study the impact of CADe system on the detection rate of polyps and adenomas in colonoscopy.	The convolutional three-dimensional (3D) neural network	Real-time Video stream	508	518	734 (486 vs 248)	39.1 vs 23.9; p <0.001; OR=1.637, 95% CI=1.201-2.220	43.7 vs 27.8; p <0.001; OR=1.57, 95% CI=1.586-2.483	36 in CADe system (control group not reported)	6.82±1.78 vs 6.74±1.62; p <0.001

Luo et al[78]	2020	Non-blinded Prospective randomised trial	To explore whether CADe could improve the polyp detection rate in the actual clinical environment.	A CNN algorithm based on a YOLO network architecture	Real-time Video stream	150	150	185 (105 vs 80)	38.7 vs 34.0; p <0.001	-	52 in CADe system (control group not reported)	6.22 ± 0.55 Vs 6.17 ± 0.52; p=0.102
Repici et al[79]	2020	Singles-blind Prospective randomised trial	To assess the safety and efficacy of a CADe system for the detection of colorectal neoplasia.	The CNN (GI-Genius; Medtronic)	Real-time Video stream	341	344	596 (353 vs 243)	54.8 vs 40.4; p <0.001; RR=1.30, 95% CI=1.14-1.45	279/341 (82) 214/344 (62)	-	417±101 seconds for the CADe group vs 435±149 for controls; P=0.1

Wang et al[80a]	2020	Singles-blind Prospective randomised trial	To investigate the impact of CADe on adenoma miss and detection rate	The artificial neural network (EndoScreener, Shanghai Wision AI Co,Ltd, Shanghai, Chin)	Real-time Video stream	184 (CADe-routine group)[b]	185 (Routine-CADe group)[c]	529 (244 vs 285)	42.39 vs 35.68; p=0.186; OR=1.327, 95% CI=0.872–2.018	63.59 vs 55.14; p=0.09; OR=1.421, 95% CI=0.936–2.157	67 in CADe system (control group not reported)	6.55 (5.34–7.77) vs 6.51 (5.45–7.57); p=0.745[d]

a: the total adenoma miss rate by CADe colonoscopy=13.89%, 95% CI=8.24%–19.54%); by routine colonoscopy=40.00%, 95% CI=31.23%–48.77%, P<0.0001. The total polyp miss rate by CADe colonoscopy=12.98%, 95% CI=9.08%–16.88%; by routine colonoscopy=45.90%, 95% CI=39.65%–52.15%, P<0.0001). Visible adenoma miss rate: Routine-CADe group=24.21% vs CADe-routine group=1.59%, p<0.001; Visible polyp miss rate: Routine-CADe group=30.89% vs CADe-routine group=2.36%; p<0.001. b: it means that the colonoscopy was performed by the CADe system and then the conventional method. c: it means that the colonoscopy was performed by the conventional method and then the CADe system. d: median (interquartile range).

CADe=computer-assisted detection system; CNN=convolutional neural network; DCNN=deep learning convolutional neural network; SD=standard deviation; OR=odds ratio; RR=relative risk; CI=confidence interval.

Table 2 Summary of the non-controlled studies involving computer-aided detection (CADe) for colonoscopy.

Author	Year	Study design	System	Image modality	Number of patients/colonoscopies used for training/test datasets (total)	Number of colonoscopy/polyp images/videos used for training/test datasets	Diagnostic properties
Park and Sargent[81]	2016	Retrospective	CADe based on DCNN using a conditional random field model	Still images	35 (colonoscopy videos)	562/562 (Colonoscopy still images)	Sensitivity=86%; specificity=85%; AUC=0.8585
Fernández-Esparrach et al[73]	2016	Retrospective	CADe based on energy map	Still images	NA/24 colonoscopy videos containing 31 different polyps	**NA/Experiment A:** 612 polyp images from all 24 videos **Experiment B:** 47,886 frames from the 24 videos	**Experiment A:** accuracy= small vs all polyps= 77.5%, 95% CI=71.5%–82.6% vs. 66.2%, 95%CI=61.4%–70.7%; P <0.01 **Experiment B:** the AUC=high quality frames vs all Frames= 0.79, 95% CI=0.70–0.87 vs 0.75,

							95% CI=0.66–0.83
Yu at al[82]	2017	Retrospective	CADe based on three-dimensional (3-D) deep learning integration framework by leveraging the 3-D fully CNN (3D-FCN)	Videos	20/18 (colonoscopy videos)	3,799 frames with polyps in total	Sensitivity=71%; PPV=88%; precision=88.1%
Billah et al[83]	2017	Retrospective	CADe based on CNN and color wavelet features using a linear support vector machine	Still images	100 (colonoscopy videos for combined training and test datasets)	14,000 still images (combined for training and test datasets)	Accuracy=98.65%; sensitivity=98.79%; specificity=98.52%
Zhang et al[84]	2017	Retrospective	CADe based on DCNN	Still images	NA	2262/150 random, 30 NBI (colonoscopy still images)	Accuracy=85.9%; sensitivity=98%; PPV=99%; precision=87.3%; recall rate=87.6%; AUC=1.0

Wang et al[85]	2018	Retrospective	CADe based on DNN	Still images	1,290/1,138 (2428) patients	27,113/5,545 (colonoscopy images)	Sensitivity=94.38%, 95% CI=93.80%-94.96% in images with polyp; AUC=0.984
Misawa et al[34]	2018	Retrospective	CADe based on CNN	Videos	59/14 (73)	411/135 (colonoscopy videos containing 150 polyps)	Per-polyp Sensitivity=94%; per-frame sensitivity=90%; specificity=63.3%; accuracy=76.5%; false positive rate=60%; AUC=0.87
Yamada et al[33]	2018	Retrospective	CADe based on DNN	Videos	NA/77 (number of videos)	13,983/4,840 (colonoscopy videos)	Sensitivity=97.3%, 95% CI=95.9%–98.4%; specificity=99.0%, 95% CI=98.6%–99.2%; AUC=0.975, 95% CI=0.964–0.986)
Urban	2018	Retrospective	CADe based on	Videos	Several training and validation sets:		Sensitivity=96.9%;

et al[35]			deep learning CNN		1) Cross-validation on the 8,641 images 2) Training on the 8,641 images and testing on the 9 videos, 11 videos, and independent dataset 3) Training on the 8,641 images and 9 videos and testing on the 11 videos and independent dataset		specificity:95% AUC=0.991; accuracy=96.4 %; false positive rate=7%
Klare et al[37]	201 9	Prospectiv e	automat ed polyp detection software (“KoloPol ,” Fraunhof er IIS, Erlangen, Germany) based on CNN	Live colonosc opy videos	NA	NA/55 (colonoscopy videos)	Per-polyp sensitivity=75. 3%, 95% CI=62.3%-84.9%; PDR= 50.9%, 95% CI=37.1%-64.4%; ADR=29.1%, 95% CI=17.6%-42.9%
Ozawa et al[86]	202 0	Retrospect ive	CADe based on DCNN	Still images	12,895 patients	16,418/7,077	Sensitivity=92 %; positive predictive value=86%; accuracy=83%; identified adenomas=97 %

CADe=computer-assisted detection system; CNN=convolutional neural network; DCNN=deep learning convolutional neural network; AUC=Area Under the Receiver Operating Characteristic curve; PPV=positive predictive value; NPV=negative predictive value; PDR=polyp detection rate; ADR=adenoma detection rate; CI=confidence interval.

Table 3 Summary of the non-controlled studies involving computer-aided diagnosis (CADx) for colonoscopy including studies with combined detection and diagnosis systems (CADx and CADe).

Author	**Year**	**Study design**	**Study aim**	**System**	**Number of patients/colonoscopies used for training/test datasets (total)**	**Number of colonoscopy/polyp images/videos used in training/test datasets**	**Diagnostic properties**
Tischendorf et al[38]	2010	Prospective pilot	Distinguishing adenomas from non-adenomas	CADx based on SVMs	NA/128 Colonoscopy videos	NA/209 polyps containing 160 neoplastic and 49 non-neoplastic polyps in the test dataset	**CADx:** sensitivity=90%, specificity=70%, correct classification rate=85.3%. **Consensus decision between the human** **Observers:** sensitivity=93.8%, specificity=85.7%, correct classification rate=91.9%. **"Safe" decision, when there**

							was interobserver discrepancy: sensitivity=96.9%, specificity=71.4%, correct classification rate=90.9%
Aihara et al[47]	2013	Prospective	Distinguishing neoplastic from non-neoplastic lesion	CADx based on numerical color analysis of autofluorescence endoscopy as an Adobe AIR application	NA/32 patients in the test dataset	NA/102 lesions containing 75 neoplastic lesions in the test dataset	Sensitivity=94.2%; specificity=88.8%, PPV=95.6%; NPV=85.2%
Mori et al[87]	2015	Retrospective pilot	Distinguishing small (≤10 mm) neoplastic from non-neoplastic lesion	CADx (EC-CAD) based on CNN	NA/152 patients in the test dataset	NA/176 small polyps in the test dataset containing 137 neoplastic and 39 non-neoplastic polyps for the test dataset	Accuracy=89.2%, 95% CI=83.7%-93.4%; Sensitivity= 92.0%, 95% CI=86.1%-95.9%; specificity of 79.5%, 95% CI=63.5%-90.7%

Kuiper et al[49]	2015	Retrospective	Distinguishing small (≤9 mm) neoplastic from non-neoplastic lesion	CADx (WavSTAT) based on CNN	NA/87 patients in the test dataset	NA/207 small lesions in the test dataset	Accuracy= 74.4%, 95% CI=68.1%–79.9%; sensitivity=85.3%, 95 % CI=0.78 – 0.90; specificity=58.8%, 95% CI=0.48 – 0.69; PPV=74.8 %, 95% CI=0.67 – 0.81; NPV= 73.5%; accuracy of on-site recommended surveillance interval=73.7%
Misawa et al	2016	Retrospective	Distinguishing neoplastic from non-neoplastic lesion categorized	CADx based on support vector machines (SVMs)	NA	979 images containing 381 non-neoplasms and 598 neoplasms in the training dataset/100 images containing 50 non-neoplasms and 50	Accuracy=90.0%, 95% CI=82.4–95.1; sensitivity=84.5%, 95% CI=72.6–92.7; specificity=97.6%, 95% CI=87.4–99.9; PPV= 98.0%, 95% CI=89.4–99.9; NPV=82.0%, 95% CI=68.6–91.4

						neoplasms in the test dataset	
Byrne et al[51]	2018	Retrospective	Distinguishing neoplastic from non-neoplastic lesions	CADx + CADe based on an improved DCNN model using NBI	NA	NA/21,804 unseen frames in the test dataset	Accuracy=99.94%; sensitivity=95.95%; specificity=91.66%; NPV=93.6%; prediction of polyp videos= 97.6%
Mori et al[48]	2018	Prospective	Distinguishing diminutive (≤5 mm) neoplastic from non-neoplastic lesions	CADx based on support vector machines (SVMs) used with NBI and endocytoscope	NA/791 patients in the test dataset	61,925 /466 polyps from 325 patients in the test dataset	**CADx-NBI :** sensitivity=92.7%, 95% CI=89.1–95.4; specificity=89.8%, 95% CI=84.4–93.9; PPV= 93.7%, 95% CI=90.2–96.2; NPV=88.3%, 95% CI=82.7–92.6. **CADx-endocytoscope:** sensitivity=91.3%, 95% CI=87.5–94.3; specificity=88.7%, 95% CI=83.1–93.0; PPV=

							92.9%, 95% CI=89.3–95.6; NPV=86.3%, 95% CI=80.4–90.9
Byrne et al[45]	2019	Retrospective	Distinguishing diminutive (≤5 mm) neoplastic from non-neoplastic lesions	CADx based on DCNN		**Training dataset:** 60089 frames from 223 polyp videos (29% NICE type 1, 53% NICE type 2 and 18% of normal mucosa with no polyp)/**validation dataset:** 40 videos (NICE type 1, NICE type 2 and two videos of normal mucosa)/**test dataset:** 125 consecutively identified diminutive	Accuracy=94%, 95% CI=86%-97%; sensitivity=98%, 95% CI=92%- 100%; Specificity=83%, 95% CI=67%-93%; NPV=97%; PPV=90%

						polyps, comprising 51 hyperplastic polyps and 74 adenomas	
Song et al[88]	2020	Retrospective	Distinguishing adenomas from SPs	CADx based on DCNN	NA	12480 image patches of 624 polyps/two test datasets of 545 polyp	Agreement between the true polyp histology CADx=0.614–0.642; accuracy=81.3–82.4%; sensitivity=82.1%; specificity=93.7%; PPV=78%; NPV=95%; the AUC=0.93–0.95, 0.86–0.89, and 0.89–0.91 for serrated polyps, benign adenoma/mucosal or superficial submucosal cancer, and deep submucosal cancer, respectively

Kudo et al[89]	2020	Retrospective	Distinguishing small (≤ 10 mm) neoplastic from non-neoplastic lesions	The EndoBRAIN system (CADx + CADe based on DCNN)	NA/89 patients test set	69,142 images taken at 520-fold magnification and 2,000 polyps/100 lesions (≤ 10 mm) in the test dataset	**CADe:** accuracy=98%, 95% CI=97.3%–98.6%; sensitivity=96.9%, 95% CI=95.8%–97.8%; specificity=100%, 95% CI=99.6%–100%; PPV=100%, 95% CI=99.8%–100%; NPV=94.6%, 95% CI=92.7%–96.1%; **CADx:** accuracy=96%, 95% CI=95.1%–96.8%; sensitivity=96.9%, 95% CI=95.8%–97.8%; specificity=94.3%, 95% CI=92.3%–95.9%; PPV=96.9%, 95% CI=95.8%–97.8%; NPV=94.3%, 95% CI=92.3%–95.9%

CADe=computer-assisted detection system; CADx=computer-assisted diagnosis system; CNN=convolutional neural network; DCNN=deep learning convolutional neural network; AUC=Area Under the Receiver Operating Characteristic curve; PPV=positive predictive value; NPV=negative predictive value; SVM=support vector machine; SP=serrated polyps; CI=confidence interval.

Table 4 Commercially available computer-assisted colonoscopy tools that have cleared regulatory approval.

Computer-assisted system	**Product**	**Manufacturer**	**Year of regulatory approval**	**Place of regulatory approval**
CADx	EndoBRAIN	Cybernet System Corp. / Olympus Corp.	2018	Japan
CADe	GI Genius	Medtronic Corp.	2019 in Europe; 2021 in US	Europe/US
CADe	ENDO-AID	Olympus Corp.	2020	Europe
CADe/CADx	CAD EYE	Fujifilm Corp.	2020	Europe/Japan
CADe	DISCOVERY	Pentax Corp.	2020	Europe
CADe	EndoBRAIN-EYE	Cybernet System Corp. / Olympus Corp.	2020	Japan
CADe	EndoAngel	Wuhan EndoAngel Medical Technology Company	2020	China
CADe	EndoScreener	WISION A.I.	2020	China
CADx	EndoBRAIN-PLUS	Cybernet System Corp. / Olympus Corp.	2020	Japan
CADx	EndoBRAIN-UC	Cybernet System Corp. / Olympus Corp.	2020	Japan
CADe	WISE VISION	NEC Corp.	2021	Europe/Japan
CADe	ME-APDS	Magentiq Eye	2021	Europe

CADe	CADDIE	Odin Vision	2021	Europe

CADe=computer-assisted detection system; CADx=computer-assisted diagnosis system

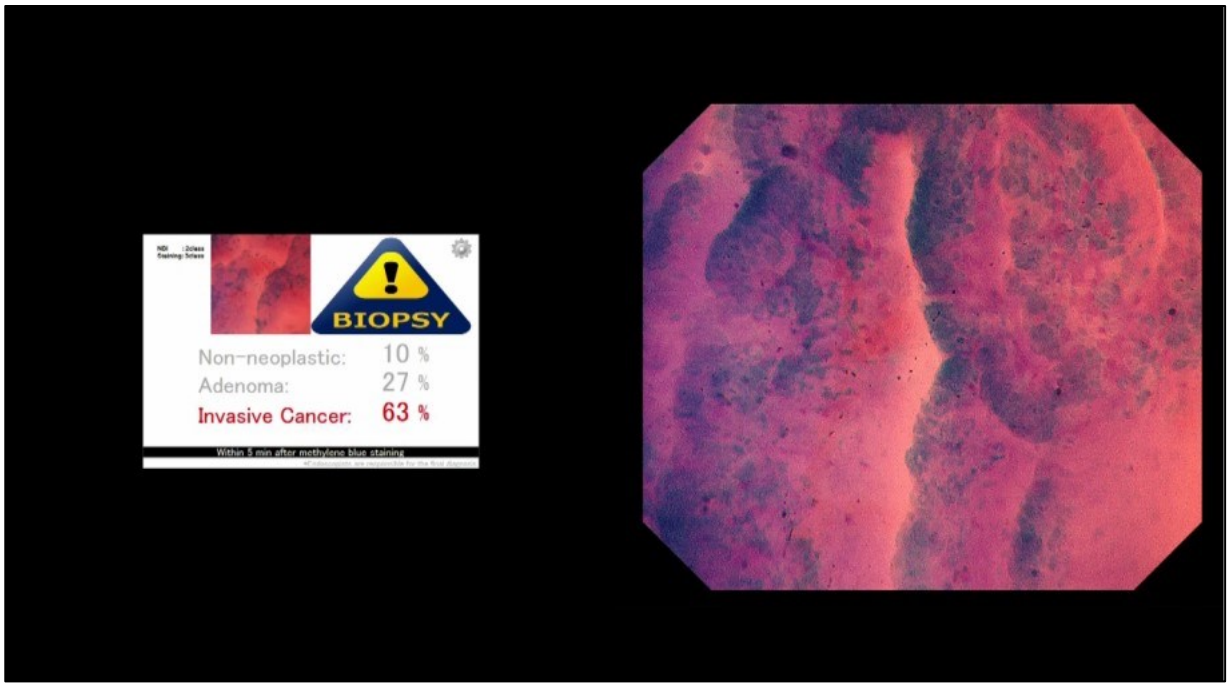


Figure 1 Prediction of colorectal polyp histology by the ENDOBRAIN computer-aided classification system for colonoscopy.

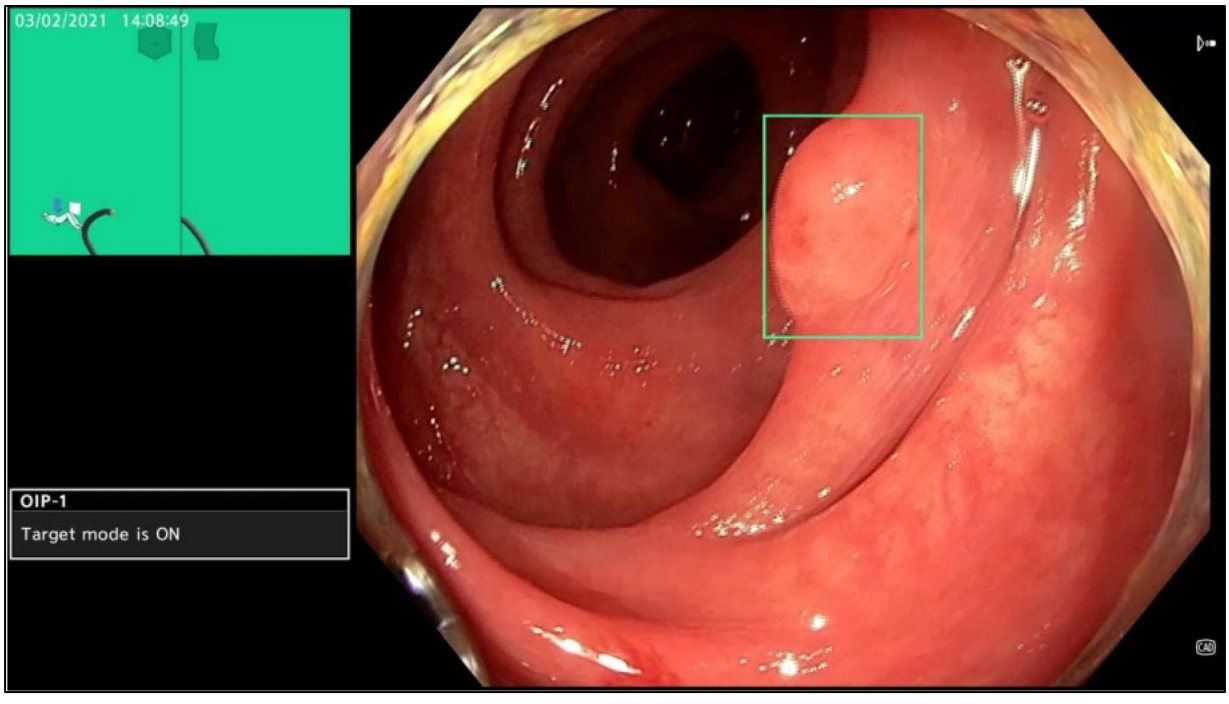


Figure 2 Detection of a colorectal polyp by the ENDOAID computer-aided detection system for colonoscopy. The green box delineates the area containing a polyp.

Chapter 7 – Article 7

Automated Detection of Anatomical Landmarks During Colonoscopy Using a Deep Learning Model

Mahsa Taghiakbari,[1,2] Sina Hamidi Ghalehjegh,[3] Emmanuel Jehanno,[3] Tess Berthier,[3] Lisa di Jorio,[3] Saber Ghadakzadeh,[3] Alan Barkun,[4] Mark Takla,[1,2] Mickael Bouin,[2,5] Eric Deslandres,[5] Simon Bouchard,[5] Sacha Sidani,[5] Yoshua Bengio,[1] Daniel von Renteln[2,5]

[1]University of Montreal, Montreal, Quebec, Canada; [2]University of Montreal Hospital Research Center (CRCHUM), Montreal, Quebec, Canada; [3]Imagia Canexia Health Inc., Montreal, Canada; [4]Division of Gastroenterology, McGill University Health Center, McGill University, Montreal, Quebec, Canada; [5]Division of Gastroenterology, University of Montreal Hospital Center (CHUM), Montreal, Quebec, Canada

Abstract

Background and aims: Identification and photo-documentation of the ileocecal valve (ICV) and appendiceal orifice (AO) confirm completeness of colonoscopy examinations. We aimed to develop and test a deep convolutional neural network (DCNN) model that can automatically identify ICV and AO, and differentiate these landmarks from normal mucosa and colorectal polyps.

Methods: We prospectively collected annotated full-length colonoscopy videos of 318 patients undergoing outpatient colonoscopies. We created three non-overlapping training, validation, and test datasets with 25,444 unaltered frames extracted from the colonoscopy videos showing four landmarks/image classes (AO, ICV, normal mucosa, and polyps). A DCNN classification model was developed, validated, and tested in separate datasets of images containing the four different landmarks.

Results: After training and validation, the DCNN model could identify both AO and ICV in 18 out of 21 patients (85.7%). The accuracy of the model for differentiating AO from normal mucosa, and ICV from normal mucosa were 86.4% (95% CI 84.1% to 88.5%), and 86.4% (95% CI 84.1% to 88.6%), respectively. Furthermore, the accuracy of the model for differentiating polyps from normal mucosa was 88.6% (95% CI 86.6% to 90.3%).

Conclusion: This model offers a novel tool to assist endoscopists with automated identification of AO and ICV during colonoscopy. The model can reliably distinguish these anatomical landmarks from normal mucosa and colorectal polyps. It can be implemented into automated colonoscopy report generation, photo-documentation, and quality auditing solutions to improve colonoscopy reporting quality.

KEYWORDS: Artificial intelligence; Colonoscopy; Ileocecal valve; Deep learning; Colorectal polyp; Endoscopy.

1. Introduction

Colonoscopy is a key component of effective colorectal cancer (CRC) prevention programs.[1, 2] A high-quality colonoscopy is achieved through a complete examination that results in a high adenoma detection rate (ADR), which reduces the risk of patients developing interval CRC.[3-5] As colonoscopy is operator dependent, multiple gastroenterology initiatives have recommended that endoscopists achieve minimum performance scores. This is represented through a cecal intubation rate (CIR) of >90%.[3] In order to demonstrate cecal intubation and completeness of the examination, current guidelines request identification and photo-documentation of the ileocecal valve (ICV) and appendiceal orifice (AO).[3, 6] Recent advancements in artificial intelligence (AI) and the development of the deep convolutional neural network (DCNN) allow for real-time image processing during colonoscopy. This enables automatic detection of anatomical structures during live endoscopies. To date, AI has mainly assisted endoscopists in the detection and classification of colorectal polyps.[7-9] We hypothesized that an AI-empowered solution could help us automatically differentiate anatomical landmarks such as AO and ICV from polyps and normal colon mucosa. Such an AI solution could be incorporated into colonoscopy report-generating software, help with automated photo-documentation, or be used for quality auditing. Therefore, we conducted a study developing a DCNN-based model to differentiate the AO, ICV, and polyps from normal colon mucosa, and to confirm automated detection of AO and ICV in a test set.

2. Methods

2.1 Study Population

We prospectively enrolled 358 consecutive patients aged 45–80 years who attended the Centre Hospitalier de l'Université de Montréal (CHUM) for an elective colonoscopy between January and October 2021. Exclusion criteria were explained in the **Supplementary File**. Additionally, colonoscopy videos in which technical failures led to problems recording the colonoscopy procedure were also excluded (n = 17). Thus, colonoscopy videos from 318 patients were included in the final analyses. All included patients signed informed consents for study participation, video recording, and further analyses of the videos. The study protocol was

approved by the local ethics board (IRB #: 20.198) and was registered at https://clinicaltrials.gov/ (NCT04586556).

2.2 Study Procedure

All colonoscopies were performed by five board-certified gastroenterologists according to the current standard of care using standard high-definition colonoscopes (Olympus 190 series; Olympus Corp., Center Valley, PA, USA).[3] The colonoscopy videos were recorded using Medicapture USB 300 devices (high definition, 1080, H.264/MPEG4) and stored on a hard drive. The endoscopists were instructed to use narrow-band imaging for performing optical diagnosis at their discretion. Endoscopists removed detected polyps using standard polypectomy techniques, and the specimens were sent to the local histopathology laboratory for histology assessment. All patients were followed up after 2 weeks to inquire about delayed adverse events. No severe adverse events were reported. All videos were deidentified by removing any patient identifier information before being permanently stored on a local hard drive. A research assistant attended each colonoscopy procedure to document all relevant study steps on standardized case report forms. The research assistant started a stopwatch function upon colonoscope insertion into the rectum to enable documentation of the exact withdrawal time and moment of landmark detection in order to create annotated video files.

Based on the recommendation of the Canadian Association of Gastroenterology[10] for standard colonoscopy procedures, the following data were collected. 1) Patient demographic and clinical characteristics, including age, sex, body mass index, family history of CRC, colonoscopy indication, and ASA classification. 2) General procedural data, including date and time of the procedure and the endoscopist's name. 3) Colonoscopy characteristics, including bowel preparation quality (poor vs. adequate, defined as an overall BBPS score >6, and >2 for each colon segment[11]), the exact time of colonoscope insertion into the rectum, the exact time of identifying important anatomical landmarks (i.e., AO, ICV), cecal intubation (as a surrogate for complete colonoscopy, yes/no), the exact time of starting withdrawal of the colonoscope, the exact time the colonoscope reached and was removed from the rectum, and withdrawal time (defined as the time required to withdraw the colonoscope from cecal intubation to removal from the anus). 4) Polyp-related characteristics, including the exact time of detection of each polyp (if multiple), and anatomical location, size, and morphology (according to the Paris

classification,[12] polypoid/non-polypoid) of each polyp. We dedicated a specific code to each endoscope and patient to avoid confusion. Therefore, all collected data on the case report forms were anonymized before being transferred to an electronic database.

2.3 Model Training and Validation

We trained a DCNN AI model on 21,503 unaltered frames extracted from the recorded colonoscopy videos of 272 patients, and validated and tested the model on 1924 (25 patients) and 2017 (21 patients) unaltered frames, respectively. **Supplementary Table 1** shows the detailed patient demographic and procedural characteristics used in each dataset. All frames were extracted from the white-light colonoscopies, and all narrow-band imaging frames were excluded. We followed the procedure shown in **Fig. 1** to extract the required frames for training and testing the AI model. The model was trained to distinguish between four distinct landmarks: 1) AO, 2) ICV, 3) polyp, and 4) normal mucosa. For each landmark, we extracted an average of 30 frames for each time of its appearance. As consecutive frames within a video are correlated, we introduced a stride of 4 frames (i.e., the amount of movement over the frames of a video) for the AO, ICV, and polyp landmarks, and a random stride of between 4 and 15 frames for the normal mucosa landmark during the frame extraction. This was to increase the exposure of the model to higher variability among non-consecutive frames.

As the annotation for timing of landmark detection in real-time might not be precise, there was a possibility that some of the extracted frames would not contain their corresponding landmarks. Furthermore, because of the movement of the colonoscope inside the colon, sometimes the landmark of interest might disappear from the field of view for a short period of time. Therefore, to ensure that we used labeled frames for model training correctly, all the extracted frames were reviewed and annotated by a team of three clinicians (MT, MT, DvR). Using a quality assessment tool, the clinicians examined a total of 86,754 frames (7982 AO, 8374 ICV, 32,971 polyps, and 37,427 normal mucosa) and verified whether or not the frame contained one unique landmark. If a frame was too blurry or contained two landmarks, or a very small portion of a landmark from which even an expert clinician could not locate the object, the frame was discarded. After performing the verification process, 25,444 frames (2914 AO, 2606 ICV, 14,772 polyps, and 5152 normal mucosa) were accepted to be used for model training, validation, and testing (**Table 1**).

The training, validation, and test datasets did not overlap (details provided in **Supplementary Table 1**).

2.4 DCNN-based AI Model

The DCNN model used in the current study is an off-the-shelf network based on the Inception V3 architecture[13] and pre-trained on the ImageNet dataset.[14] We applied a transfer learning technique to fine-tune the model parameters to the endoscopic images using a cross-entropy loss function and back-propagation algorithm.[15] The model was trained to distinguish between AO, ICV, polyp, and normal mucosa. The images associated with different classes were fed to the model in equal proportions to keep the balance across the four classes during the training phase. For all experiments, we used an Adam optimizer with a learning rate of 0.0002. We used a learning rate scheduler with patience of 5 and a factor of 0.5 to decrease the learning rate when the validation accuracy stopped improving. Because of the small volume of data available, different techniques were used to decrease the over-fitting of the model, such as different data-augmentation techniques, which were applied to each frame, thus introducing more variability and richer diversity to the model.[16] This included 90% to 100% horizontal and vertical scaling, 0-to-5-degree rotation, –5% to 5% horizontal and vertical translation, 95% to 105% color saturation adjustment, 95% to 105% color brightness adjustment, random horizontal and vertical flipping, –3% to 3% horizontal and vertical shearing, 0 to 1% perspective, and 0 to 2% sharpening. We used L2 regularization with a penalty of 0.001, a drop-out before the Softmax layer with a drop rate of 0.8, and an early-stopping technique. The model training, validation, and testing were performed using an NVIDIA Tesla V100 GPU with 32 GB of memory.

2.5 Study Outcomes

The primary outcome was the proportion of patients in whom the AI model could identify both ICV and AO, and differentiate them from polyps and normal mucosa, with an accuracy of detecting both AO and ICV above a threshold of 40% (representing a value in which reliable identification of the landmarks can be assumed without increasing false-positive alerts). The secondary outcome was the accuracy of the AI model in differentiating AO (vs. normal mucosa) compared with frames annotated by expert endoscopists, which were used as the reference.

Other outcomes included: 1) the accuracy of the AI model to differentiate ICV (vs. normal mucosa) compared with the expert-annotated frames; 2) the accuracy of the AI model to differentiate polyp (vs. normal mucosa); 3) the accuracy of the AI model to differentiate normal mucosa, defined as the colonoscopy images containing no other landmarks (i.e., OA, ICV, polyp, diverticulum); 4) the accuracy of the model to differentiate between AO, ICV, polyp, and normal mucosa when >1 landmark appeared in an image; 5) other diagnostic characteristics of the AI model for differentiating each landmark mentioned above, including sensitivity, specificity, negative and positive predictive values, and the area under the receiver operating characteristic curve (AUC); 6) the false-positive detection rate for each landmark.

2.6 Statistical Analysis

All confidence intervals were computed using Clopper-Pearson interval method for calculating binomial confidence intervals using the extracted confusion matrices from the model that categorized the predictions of each landmark in each image against the actual annotated images in the test dataset. The R programming language (R Core Team, 2020) was used for statistical computing of all diagnostic performance values and confidence intervals.

3. Results

A total of 2017 frames were used to test the performance of the AI model on unseen data (**Table 1**). Both AO and ICV could concomitantly be detected in 18 out of 21 patients (85.7%; 95% CI 63.7% to 97.0%) if accuracies were above the threshold of 40%. **Table 2** shows details of the co-detection of both AO and ICV by the AI model.

The accuracy of the model for differentiating AO, ICV, and polyps from normal mucosa was 86.4% (95% CI 84.1% to 88.5%), 86.4% (95% CI 84.1% to 88.6%), and 88.6% (95% CI 86.6% to 90.3%), respectively (**Table 3**). The accuracy of the model was 90.8% (95% CI 89.2% to 92.3%) for differentiating AO from ICV and normal mucosa, and 93.0% (95% CI 91.5% to 94.3%) for differentiating ICV from AO and normal mucosa. The per-patient accuracies are presented in the **Supplementary file**.

The false-positive rates of detecting AO, ICV, and polyp (vs. normal mucosa) were 11.7%, 14.7%, and 10.9%, respectively. The inference time of the model for each image frame was around 100 ms.

Table 3 shows detailed results of the AI model performance in the test dataset. **Fig. 2** shows the AUC of the AI algorithm for detecting each anatomical landmark in the test set.

4. Discussion

To the best of our knowledge, this study describes the first AI model to use a DCNN to automatically detect AO and ICV, and differentiate them from polyps and normal colon mucosa. Results showed that the model was able to differentiate these landmarks from polyps and normal mucosa with high accuracy. The model automatically detected both AO and ICV in 86% of patients in our test set. It also demonstrated a high ability (AUCs ≥90%) to distinguish AO, ICV, and polyps from normal mucosa in the test set. The required images for developing this model were prospectively obtained from a cohort of consecutive patients undergoing screening, surveillance, or diagnostic colonoscopies by multiple endoscopists, thus, enhancing generalizability, and reducing training, selection, and operator bias.

The U.S. Multi-Society Task Force on Colorectal Cancer suggests that visualization and documentation of the ICV and AO with photo-documentation is compulsory and an essential part of a high-quality colonoscopy.[17] DCNN-based AI-assisted colonoscopy is a state-of-the-art system that already assists endoscopists with polyp detection and classification through commercially available solutions.[18] Adding an AI module confirming completeness of a colonoscopy procedure seems a logical next step in the evolution of AI-assisted colonoscopy practice, as performing a complete colonoscopy is a vital prerequisite for a high ADR, and for minimizing the risk of interval cancer.[3, 19, 20] Therefore, we aimed to create a model that can reliably detect both structures (e.g., AO and ICV) and distinguish them from normal mucosa and polyps. The combined detection of AO and ICV also avoids misreading of a diverticulum as confirmation of a complete colonoscopy.

Few studies have developed and tested new AI and non-AI approaches for identifying anatomical landmarks. These studies have the following major drawbacks: a small sample size, use of image-

based data, low ADR, lack of testing in an independent dataset, confusing alarm system, lack of DCNN technology, and never exceeding a prototype. One initial research used the non-AI K-mean classifier technique to automatically classify the 800 manually-annotated images derived from five colonoscopies into either appendix image or non-appendix image classes.[21] Although the model accuracy was promising (90%), the exclusion of the images containing tangential AO and a relatively high false positive classification rate precluded further clinical application of the model. Likewise, Wang et al used two non-AI algorithms to automatically detect AO.[22] The initial algorithm distinguished images containing AO from others by analyzing geometric shape, saturation, and intensity changes along the edge's cross-section. The second algorithm identified videos containing an appendix by analyzing frame intensity histograms to detect a near-camera pause during AO inspection. The average sensitivity and specificity of the first algorithm was 96.86% and 90.47%, respectively. The average accuracy of the second algorithm for detecting appendix videos was 91.30%. However, this study used only 23 colonoscopy videos and was not validated in an independent dataset, which limits its generalizability. Recent advances in AI and deep learning have led to a growing consensus on the possibility of automatic detection of a complete colonoscopy. An AI model using CNN algorithm was developed using 3,222 images extracted from 35 colonoscopy videos to detect the AO irrespective of bowel preparation.[23] The accuracy and AUC of this model was 94% and 98%, respectively. However, this model has never been tested in practice. Another CNN model was trained using 6,487 colon images prospectively obtained from over 300 colonoscopy procedures and annotated by two expert endoscopists for anatomic landmarks, lesions, and bowel preparation adequacy.[24] This model intended to automatically calculate CIR and withdrawal time. The model accuracy was 88% when trained on all images including unprocessed and suboptimal-quality images, but increased to 98% accuracy and 99% AUC when trained on a subset of 1000 optimal images. The model's effectiveness in real-time colonoscopy has remained untested. Furthermore, a study developed both image-based and video-based CNN models to calculate withdrawal time from the timepoint of detecting the ICV. The highest accuracy of 99.6% was achieved with an image-based dataset, but only 70% accuracy was obtained with a video-based dataset.[25] Another recent study trained an AI algorithm using colonoscopy images (not obtained from a prospective patient cohort) to detect the AO, resulting in a 95% AUC in the test dataset.[26]

Our DCNN model could be integrated into colonoscopy reporting software. We imagine future applications that could automatically document landmark identification timepoints and generate automated reports post-colonoscopy, including all relevant procedural steps (identification time of ICV, AO, polyps), along with photo-documentation and withdrawal time calculations. Other potential applications include auditing tools. Previous attempts to develop and link auditing tools to real-time endoscopy practice have been challenging, mainly due to the significant administrative and budgetary burden placed on hospitals and the lack of structured endoscopic educational systems. To our knowledge, no auditing system has been designed and tested to provide simultaneous and automatic feedback on procedure quality and polyp classification as well as generate electronic reports. Our proposed model can be integrated into endoscopy practice as a didactic or practice audit system, used by experts and trainees, for providing a unified screening, intervention, and educational modality. Moreover, this system offers the potential to be coupled with the computer-assisted modules to obviate the bias raised by self-reporting and self-evaluation of practice quality.

The strengths of this study include the use of a large number of colonoscopy videos prospectively collected by multiple endoscopists, resulting in a mixture of colonoscopy findings (i.e., normal mucosa and polyps) and a high number of extracted frames. This model worked with unprocessed frames, and used the polyp images regardless of the polyp anatomical location and histology. Two experts reviewed all colonoscopy images, and a third expert endoscopist made the final annotation in cases of disagreement to ensure a high inter-rater agreement. The DCNN AI model is robust as it was trained end-to-end, resulting in performing classification tasks within the same learning model. Additionally, advanced equipment (i.e., high-definition endoscopes) were used for performing and recording all colonoscopies, following recommendations to use high-definition colonoscopes for screening and surveillance colonoscopy to effectively improve detection, resulting in high-quality videos and images.

However, the study does present some limitations. We included only colonoscopies of patients with adequate bowel preparation. As a result, it is necessary to further examine the generalizability of this model in real-time clinical application, ideally through a multicenter clinical trial using a higher number of colonoscopies. Furthermore, our model does not aim to distinguish anatomical landmarks from other lesions such as diverticula. Moreover, the total processing time was 100 ms, which is longer than the 33 ms of recommended inference time per

frame for real-time system implication. Nonetheless, the strategies followed in this research for AI model training did not include advanced machine learning optimization and pruning techniques to decrease inference time. Further research should incorporate appropriate techniques to enhance model's inference time and detection accuracy. Additionally, it is recommended to validate the model on a video-based dataset to evaluate its performance in operational context.

5. Conclusion

To conclude, we developed a DCNN model that can reliably identify both AO and ICV in a test set of images from colonoscopy procedures. Furthermore, the DCNN model could distinguish AO and ICV from normal mucosa and colorectal polyps with high accuracy. We believe that this study is the first crucial step in creating a better automated colonoscopy reporting and auditing system that can deliver a colonoscopy report immediately after a procedure, including automated photo-documentation of anatomical landmarks and polyps.

6. References

1. Brenner DR, Weir HK, Demers AA, et al. Projected estimates of cancer in Canada in 2020. CMAJ. 2020;192:E199-E205.
2. Ponugoti PL, Cummings OW, Rex DK. Risk of cancer in small and diminutive colorectal polyps. Dig Liver Dis. 2017;49:34-7.
3. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. Gastrointest Endosc. 2015;81:31-53.
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. Faigel DO, Pike IM, Baron TH, et al. Quality indicators for gastrointestinal endoscopic procedures: an introduction. Gastrointest Endosc. 2006;63:S3-9.
6. Marques S, Bispo M, Pimentel-Nunes P, Chagas C, Dinis-Ribeiro M. Image Documentation in Gastrointestinal Endoscopy: Review of Recommendations. GE Port J Gastroenterol. 2017;24:269-74.
7. Taghiakbari M, Mori Y, von Renteln D. Artificial intelligence-assisted colonoscopy: A review of current state of practice and research. World J Gastroenterol. 2021;27:8103-22.
8. Byrne MF, Shahidi N, Rex DK. Will Computer-Aided Detection and Diagnosis Revolutionize Colonoscopy? Gastroenterology. 2017;153:1460-4 e1.
9. Hoerter N, Gross SA, Liang PS. Artificial Intelligence and Polyp Detection. Curr Treat Options Gastroenterol. 2020;18:120-36.
10. Beaulieu D, Barkun AN, Dubé C, Tinmouth J, Hallé P, Martel M. Endoscopy reporting standards. Can J Gastroenterol. 2013;27:286-92.
11. Kastenberg D, Bertiger G, Brogadir S. Bowel preparation quality scales for colonoscopy. World J Gastroenterol. 2018;24:2833-43.
12. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc. 2003;58:S3-43.
13. Szegedy C, Vanhoucke V, Ioffe S, Shlens J, Wojna Z, editors. Rethinking the inception architecture for computer vision. Proceedings of the IEEE conference on computer vision and pattern recognition; 2016.
14. Deng J, Dong W, Socher R, Li L-J, Li K, Fei-Fei L, editors. Imagenet: A large-scale hierarchical image database. 2009 IEEE conference on computer vision and pattern recognition; 2009: Ieee.
15. Rumelhart DE, Hinton GE, Williams RJJn. Learning representations by back-propagating errors. 1986;323:533-6.
16. Shorten C, Khoshgoftaar TMJJobd. A survey on image data augmentation for deep learning. 2019;6:1-48.
17. 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. Gastroenterology. 2017;153:307-23.
18. Mori YJE. Artificial intelligence and colonoscopy: the time is ripe to begin clinical trials. 2019;51:219-20.
19. Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. Ann Intern Med. 2011;154:22-30.
20. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med. 2000;343:169-74.

21. Cao Y, Liu D, Tavanapong W, Wong J, Oh J, Groen PCd, editors. Automatic Classification of Images with Appendiceal Orifice in Colonoscopy Videos. 2006 International Conference of the IEEE Engineering in Medicine and Biology Society; 2006 30 Aug.-3 Sept. 2006.
22. Wang Y, Tavanapong W, Wong JS, Oh J, de Groen PC. Detection of quality visualization of appendiceal orifices using local edge cross-section profile features and near pause detection. IEEE Trans Biomed Eng. 2010;57:685-95.
23. Low DJ, Hong Z, Khan R, Bansal R, Gimpaya N, Grover SC. Automated detection of cecal intubation with variable bowel preparation using a deep convolutional neural network. Endosc Int Open. 2021;9:E1778-E84.
24. Karnes WE, Ninh A, Dao T, Requa J, Samarasena JB. Sa1925 REAL-TIME IDENTIFICATION OF ANATOMIC LANDMARKS DURING COLONOSCOPY USING DEEP LEARNING. Gastrointestinal Endoscopy. 2018;87:AB252.
25. Li Y, Ding A, Cao Y, Liu B, Chen S, Liu X, editors. Detection of Endoscope Withdrawal Time in Colonoscopy Videos. 2021 20th IEEE International Conference on Machine Learning and Applications (ICMLA); 2021 13-16 Dec. 2021.
26. Lebedev A, Khryashchev V, Kazina E, Zhuravleva A, Kashin S, Zavyalov D, editors. Automatic Identification of Appendiceal Orifice on Colonoscopy Images Using Deep Neural Network. 2020 IEEE East-West Design & Test Symposium (EWDTS); 2020 4-7 Sept. 2020.

Table 1 Number of frames used for artificial intelligence model training, validation, and testing.

Number of Frames	Total	Rejected frames	Frames not tagged	Accepted frames	Number of frames used in training dataset	Number of frames used in validation dataset	Number of frames used in test dataset
Normal mucosa	37,427	5172	27,103	5152	4103	519	530
Polyp[a]	32,971	17,353	846	14,772	13,479	651	642
Ileocecal valve	8374	5619	149	2606	1892	322	392
Appendiceal orifice	7982	4708	360	2914	2029	432	453
Total	86,754	32,852	28,458	25,444	21,503	1924	2017

[a]All frames containing polyps were retrieved from white-light colonoscopy videos.

Table 2 The proportion of patients in the test dataset, in which the deep convolutional neural network model could identify both ileocecal valve and appendiceal orifice.

Patients	**Number of frames with AO**	**Accuracy of detecting AO, %**	**Number of frames with ICV**	**Accuracy of detecting ICV, %**
1	31	100	24	50
2	17	82.35	13	46.15
3	28	89.29	24	100
4	31	0	29	93.1
5	16	87.5	23	100
6	17	94.12	11	100
7	22	95.45	19	100
8	21	100	23	95.65
9	25	100	25	100
10	7	71.43	10	100
11	24	0	6	100
12	24	95.83	15	100
13	23	100	15	93.33
14	24	79.17	18	100

15	21	95.24	19	100
16	22	100	18	100
17	26	92.31	21	100
18	21	95.24	26	96.15
19	31	100	15	100
20	18	100	24	87.5
21	4	0	14	100

AO, appendiceal orifice; *ICV*, ileocecal valve.

Both AO and ICV could concomitantly be detected in:

1) 18 out of 21 patients (85.7%; 95% CI 63.7% to 97.0%) if accuracies were above threshold of 40%

2) 17 out of 21 patients (81.0%; 95% CI 58.1% to 94.6%) if accuracies were above threshold of 50%

3) 16 out of 21 patients (76.2%; 95% CI 52.8% to 91.8%) if accuracies were above threshold of 60%

4) 16 out of 21 patients (76.2%; 95% CI 52.8% to 91.8%) if accuracies were above threshold of 70%

5) 14 out of 21 patients (66.7%; 95% CI 43.0% to 85.4%) if accuracies were above threshold of 80%

6) 11 out of 21 patients (52.4%; 95% CI 29.8% to 74.3%) if accuracies were above threshold of 90%

Table 3 Summary of the performance of the deep convolutional neural network artificial intelligence algorithm for the test dataset.

Detected landmarks	Total number of images	Number of TP	Number of TN	Number of FP	Number of FN	sensitivity (95% CI)	specificity (95% CI)	NPV (95% CI)	PPV (95% CI)	Accuracy (95% CI)	AUC (95% CI)
Normal mucosa vs. AO	983	381	468	62	72	84.1 (80.4 to 87.4)	88.3 (85.3 to 90.9)	86.67 (83.51 to 89.42)	86.0 (82.4 to 89.1)	86.4 (84.1 to 88.5)	90.8 (88.8 to 92.8)
Normal mucosa vs. ICV	922	345	452	78	47	88.0 (84.4 to 91.1)	85.3 (82.0 to 88.2)	90.58 (87.67 to 93.0)	81.6 (77.5 to 85.1)	86.44 (84.1 to 88.6)	94.4 (93.0 to 95.8)
Normal mucosa vs. polyp	1172	566	472	58	76	88.2 (85.4 to 90.6)	89.1 (86.1 to 91.6)	86.13 (82.95 to 88.92)	90.7 (88.2 to 92.9)	88.6 (86.60 to 90.33)	94.8 (93.9 to 96.0)
Normal mucosa and ICV vs. AO[a]	1375	372	877	45	81	82.1 (78.3 to 85.5)	95.1 (93.5 to 96.4)	91.54 (89.60 to 93.23)	89.2 (85.8 to 92.0)	90.8 (89.2 to 92.3)	93.6 (92.2 to 95.0)
Normal mucosa and AO vs. ICV[a]	1375	365	914	69	27	93.1 (90.1 to 95.4)	93.0 (91.2 to 94.5)	97.13 (95.85 to 98.10)	84.1 (80.3 to 87.4)	93.0 (91.5 to 94.3)	97.6 (96.8 to 98.3)
Normal mucosa, AO and ICV vs. polyp[a]	2017	480	1294	81	162	74.8 (71.2 to 78.1)	94.1 (92.7 to 95.3)	88.87 (87.15 to 90.44)	85.6 (82.4 to 88.4)	88.0 (86.5 to 89.3)	93.4 (92.3 to 94.5)
Normal mucosa, polyp and ICV vs. AO[a]	2017	321	1509	55	132	70.9 (66.4 to 75.0)	96.5 (95.5 to 97.3)	92.96 (90.53 to 93.23)	85.4 (81.4 to 88.8)	90.7 (89.4 to 92.0)	95.3 (94.3 to 96.3)
Normal mucosa, polyp and	2017	343	1502	123	49	87.5 (83.8 to 90.6)	92.4 (91.0 to 93.7)	96.84 (95.84 to 97.65)	73.6 (69.4 to 77.6)	91.5 (90.2 to 92.7)	97.8 (97.3 to 98.3)

AO vs. ICV[a]											

[a]The numbers were aggregated at the final step after getting results.

TP/TN, true positives/negatives; *FP/TN*, false positives/negatives; *NPV*, negative predictive value; *PPV*, positive predictive value; *AUC*, area under receiver operating characteristic curve; *CI*, confidence interval; *AO*, appendiceal orifice; *ICV*, ileocecal valve.

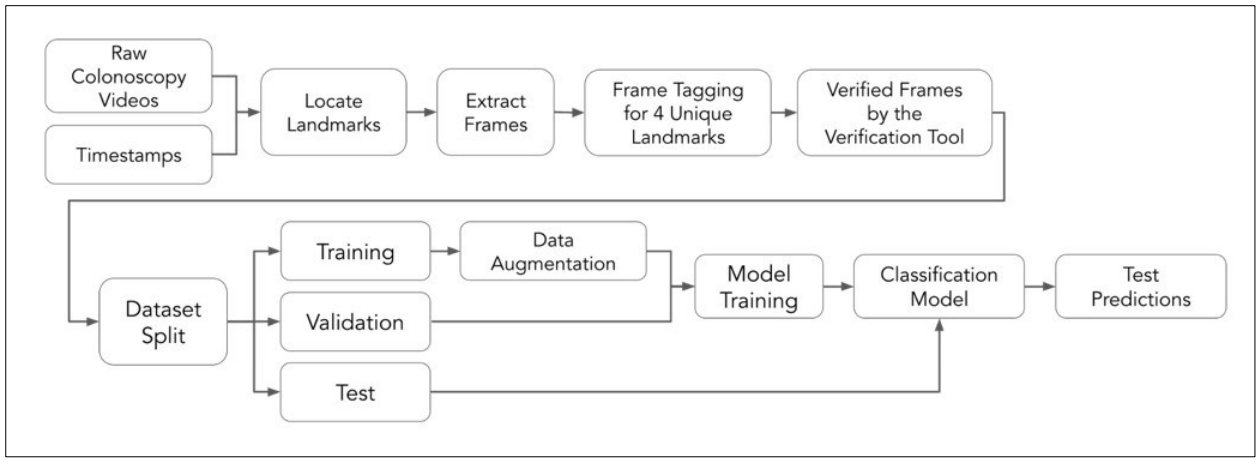


Figure 1 Illustration of data preparation, frame-by-frame landmark tagging, and quality assessment workflow for building disjoint databases for training and validation of a deep convolutional neural network classification model, and final prediction of landmarks in unseen test data.

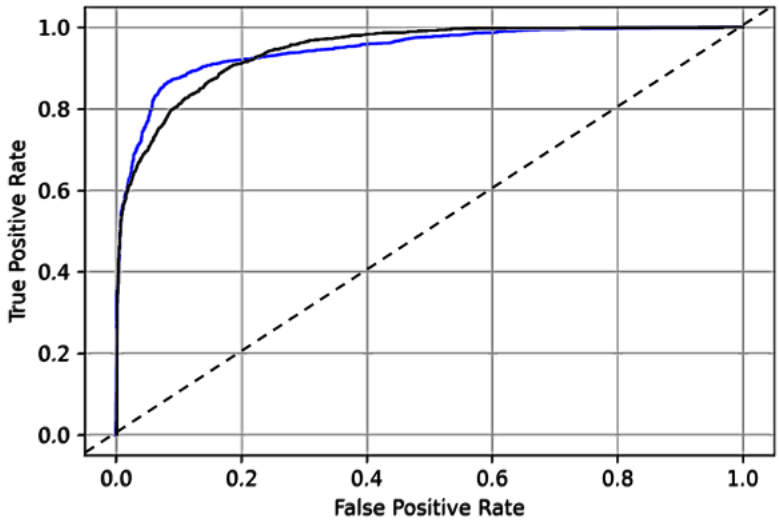


Figure 2 The area under the curve of the deep convolutional neural network model to distinguish appendiceal orifice versus ileocecal valve, and versus normal mucosa (blue line; AUC = 94.51 [95% CI 93.77 to 95.25]), and the appendiceal orifice versus ileocecal valve versus polyp, and versus normal mucosa (black line; AUC = 94.41 [95% CI 93.90 to 94.93]). The black dashed line represents the reference line.

Supplementary Material 1 Exclusion Criteria

Patients with active coagulopathy, inflammatory bowel diseases, familial polyposis syndrome, poor general health (defined as an American Society of Anesthesiologists [ASA] physical status class >3), need for emergency colonoscopies, or those who were hospitalized or in the emergency room were excluded from the study. Patients with inadequate bowel cleanliness, defined as a total Boston Bowel Preparation Score (BBPS) <6 or score <2 in the right segment[1], and those with a history of hemicolectomy were also excluded (n = 23).

1. Kastenberg D, Bertiger G, Brogadir S. Bowel preparation quality scales for colonoscopy. World J Gastroenterol 2018; 24(26): 2833-43.

Supplementary Material 2 Per-patient accuracy of the deep convolutional neural network artificial intelligence algorithm for the test dataset.

All values are presented as percentage (%). (TP: true positive; FP: false positive; CI: confidence interval; AO: appendiceal orifice; ICV: ileocecal valve)

AO vs normal mucosa:

Threshold: 10.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 20.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 30.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 40.0, TP: 20, FP: 1, Accuracy: 95.24, 95% CI: 76.18 to 99.88

Threshold: 50.0, TP: 20, FP: 1, Accuracy: 95.24, 95% CI: 76.18 to 99.88

Threshold: 60.0, TP: 19, FP: 2, Accuracy: 90.48, 95% CI: 69.62 to 98.83

Threshold: 70.0, TP: 18, FP: 3, Accuracy: 85.71, 95% CI: 63.66 to 96.95

Threshold: 80.0, TP: 17, FP: 4, Accuracy: 80.95, 95% CI: 58.09 to 94.55

Threshold: 90.0, TP: 13, FP: 8, Accuracy: 61.9, 95% CI: 38.44 to 81.89

ICV vs normal mucosa:

Threshold: 10.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 20.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 30.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 40.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 50.0, TP: 20, FP: 1, Accuracy: 95.24, 95% CI: 76.18 to 99.88

Threshold: 60.0, TP: 19, FP: 2, Accuracy: 90.48, 95% CI: 69.62 to 98.83

Threshold: 70.0, TP: 17, FP: 4, Accuracy: 80.95, 95% CI: 58.09 to 94.55

Threshold: 80.0, TP: 17, FP: 4, Accuracy: 80.95, 95% CI: 58.09 to 94.55

Threshold: 90.0, TP: 12, FP: 9, Accuracy: 57.14, 95% CI: 34.02 to 78.18

Polyp vs normal mucosa:

Threshold: 10.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 20.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 30.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 40.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 50.0, TP: 20, FP: 1, Accuracy: 95.24, 95% CI: 76.18 to 99.88

Threshold: 60.0, TP: 20, FP: 1, Accuracy: 95.24, 95% CI: 76.18 to 99.88

Threshold: 70.0, TP: 19, FP: 2, Accuracy: 90.48, 95% CI: 69.62 to 98.83

Threshold: 80.0, TP: 18, FP: 3, Accuracy: 85.71, 95% CI: 63.66 to 96.95

Threshold: 90.0, TP: 14, FP: 7, Accuracy: 66.67, 95% CI: 43.03 to 85.41

Normal mucosa+ICV vs AO:

Threshold: 10.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 20.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 30.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 40.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 50.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 60.0, TP: 20, FP: 1, Accuracy: 95.24, 95% CI: 76.18 to 99.88

Threshold: 70.0, TP: 19, FP: 2, Accuracy: 90.48, 95% CI: 69.62 to 98.83

Threshold: 80.0, TP: 18, FP: 3, Accuracy: 85.71, 95% CI: 63.66 to 96.95

Threshold: 90.0, TP: 16, FP: 5, Accuracy: 76.19, 95% CI: 52.83 to 91.78

Normal mucosa+AO vs ICV:

Threshold: 10.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 20.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 30.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 40.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 50.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 60.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 70.0, TP: 21, FP: 0, Accuracy: 100.0, 95% CI: 83.89 to 100

Threshold: 80.0, TP: 18, FP: 3, Accuracy: 85.71, 95% CI: 63.66 to 96.95

Threshold: 90.0, TP: 16, FP: 5, Accuracy: 76.19, 95% CI: 52.83 to 91.78

Supplementary Table 1 Patients and procedures baseline characteristics.

Variables	Training dataset **(n = 272)**	Validation dataset **(n = 25)**	Test dataset **(n = 21)**
Age, median (IQR), years	64.0 (14.0)	65.0 (8.5)	67.0 (13.5)
Sex, n (%)			
Male	148 (54.4)	15 (60.0)	10 (47.6)
Female	124 (45.6)	10 (40.0)	11 (52.4)
Family history of CRC, n (%)			
No	199 (73.2)	18 (72.0)	14 (66.7)
Yes	56 (20.6)	6 (24.0)	7 (33.3)
Unknown	17 (6.2)	1 (4.0)	-
Colonoscopy indication, n (%)			
Screening	41 (15.1)	2 (8.0)	1 (4.8)
Positive FIT	22 (8.1)	2 (8.0)	3 (14.3)
Adenoma surveillance	128 (47.1)	14 (56.0)	9 (42.9)
CRC surveillance	9 (3.3)	-	-
Anemia/bleeding	31 (11.4)	4 (16.0)	5 (23.8)
Polypectomy	7 (2.6)	-	-
Diarrhea	5 (1.8)	1 (4.0)	2 (9.5)
Other	29 (10.7)	2 (8.0)	1 (4.8)
Endoscopy device, n (%)			
CF-HQ190L	264 (97.1)	25 (100)	20 (95.2)
PCF-H190L	4 (1.5)	-	-
Other	4 (1.5)	-	1 (4.8)

Ileocecal valve identified, n (%)			
Yes	263 (96.7)	25 (100)	21 (100)
Appendiceal orifice identified, n (%)			
Yes	257 (94.5)	24 (96.0)	21 (100)
Withdrawal time, median (IQR), minutes	9.6 (7.8)	8.4 (2.8)	12.6 (7.8)
Polyp detection rate, %	62.1	64.0	100
Number of identified polyps	473	26	41
Polyp size, median (IQR), mm	3.0 (4.0)	3.0 (2.0)	2.0 (2.5)
Paris classification, n (%)			
IP	30 (6.3)	-	2 (4.9)
IS	323 (68.3)	23 (88.5)	29 (70.7)
IIa	41 (8.7)	2 (7.7)	7 (17.1)
IIb	-	-	-
IIc	8 (1.7)	-	3 (7.3)
III	-	-	-
Pathology, n (%)			
Normal mucosa	28 (5.9)	1 (3.8)	7 (17.1)
Hyperplastic	76 (16.1)	10 (38.5)	11 (26.8)
Tubular adenoma	212 (44.8)	11 (42.3)	16 (39.0)
Tubulovillous adenoma	17 (3.6)	-	3 (7.3)
Villous adenoma	3 (0.6)	-	-

Traditional serrated adenoma	2 (0.4)	-	-
Sessile serrated polyp/adenoma	24 (5.1)	-	2 (4.9)
High-grade dysplasia	1 (0.2)	-	1 (2.4)
Other	13 (2.7)	-	1 (2.4)
Not retrieved	31 (6.6)	-	-
Missing	66 (14.0)	1 (3.8)	-

IQR, interquartile range; CRC, colorectal cancer; FIT, fecal immunologic test.

Chapter 8 – Discussion

8.1 Recent Advances in Optical Diagnosis

8.1.1 The Dilemma in Clinical Practice of Optical Diagnosis

Colonoscopy can be a potentially costly procedure due to the classic practice of removing and histologically evaluating all detected polyps regardless of the risk of malignancy.[96] A reduction in the number of histopathology examinations and an increased immediate communication of next surveillance plans to patients and their primary care physicians would result in an overall reduction in colonoscopy costs and duration without compromising the effectiveness of colonoscopy in reducing the risk of PCCRC. The broad implementation of optical diagnosis would significantly contribute to reducing the financial, environmental, and administrative burden of screening programs. In fact, the evidence supporting the benefits, feasibility and safety of optical diagnosis for diminutive colorectal polyps, as well as its comparability with the histopathology reference standard, is strong. The resect and discard approach would save more than US$1 billion annually in upfront costs by forgoing histological examinations in the U.S.[96] However, during the last decade after 2011, when the ASGE PIVI identified endoscopic polyp characterization as a key area for new endoscopic technologies, there is an ongoing debate on whether it is possible to achieve a paradigm shift in the endoscopic management of diminutive colorectal polyps.[29,40] These hesitations or reluctance about optical diagnosis are amplified by suboptimal accuracy of expert and non-expert endoscopists irrespective of the availability of ancillary devices, and the deficiency of educational and financial incentives for endoscopists. Considering the unreliability of histopathology examinations for determining the histology of 1–3 mm polyps and a higher agreement between surveillance intervals recommended based on the high-confidence optical diagnosis of 1–3 mm polyps and CADx than that of pathology results, optical diagnosis should be increasingly advocated as a valid and appropriate management of diminutive polyps 1–3 mm in size.[27,97-100] The findings of **Chapter 1** underscore the importance of using optical diagnosis for histology determination of polyps 1–3 mm in size by demonstrating a superior concordance between high-confidence optical diagnosis-based and pathology-based surveillance intervals for the 1–3 mm polyp group compared to the 1–5 mm polyp group (96.2% vs. 93.6%, respectively).

The most important factor that would disincentivize endoscopists to perform the resect and discard approach is the risk of discarding a cancer or arising cancer from the thrown out advanced polyps and its related medicolegal issues. This may lead endoscopists to refrain from discussing this option with their patients, or patients may be reluctant to undergo the resection and discarding of diminutive polyps during a colonoscopy. This flawed belief can be defied by at least two facts. First, the majority of detected colorectal polyps are diminutives with a minimal risk of malignancy.[23,28,86,101] Additionally, more than 85% of rectosigmoid diminutive polyps are hyperplastic.[102] In a prospective multicenter study, only 1.5% of polyps 1–9 mm in size detected by screening colonoscopy had advanced histological features.[22] In addition, patients considered as high-risk because of diminutive polyps with advanced histologic features were equally found to have metachronous advanced neoplasia as low-risk patients (relative risk (RR)=1.13; 95% confidence interval (CI)=0.79–1.61).[22] Second, PCCRC is primarily caused by the failure to detect a polyp or the inability to resect it completely within a safe margin, not by discarding a polyp.[74,103] Therefore, removing a polyp would eliminate the risk of cancer progression even without pathology evaluation and would not significantly alter patient outcomes, while maximizing detection and effective polypectomy would significantly improve patient outcomes. In **chapter 1**, more evidence was presented to demonstrate that the fear of misdiagnosing and/or discarding a cancer defies the evidence-based patient outcomes. In line with previous literature, the risk of advanced pathology in diminutive polyps was extremely low.[22,104,105] Only 0.5% of 1–3 mm polyps and 0.6% of 1–5 mm polyps had advanced pathology, and no cancer was detected.[105] Noteworthy, all polyps with advanced histology among 1–5 mm polyps presented a villous component and no HGD or cancer was found. Even though the 2020 USMSTF guideline considers polyps with villous components as advanced in contrast to the ESGE guideline, no evidence has been found to definitively link villous histology to an increased risk of malignancy.[106-108]

Furthermore, it was found that the common belief that patients may be mismanaged by optical diagnosis (i.e., assigned a longer surveillance interval) is an incorrect interpretation of the clinical evidence. As discussed in **Chapter 1–3**, the optical diagnosis using IEE technologies could surpass the agreement concordance of at least 90% with pathology recommended by the ASGE PIVI.[26] It was particularly highlighted in **Chapter 1** that limiting optical diagnosis to polyps 1–3 mm in size would increase the reliability of this approach. As discussed, the agreement between surveillance interval recommendations based on the high-confidence optical diagnosis of polyps and pathology-based recommendations significantly exceeded the ASGE PIVI recommended

threshold of 90% in polyps 1–3 mm in size (96.2%), which was superior to the agreement in 1–5 mm in size (93.6%). However, a lower proportion of patients (3.8%) with at least one polyp 1–3 mm in size with advanced histology would have received a delayed surveillance recommendation compared to those with at least one polyp 1–5 mm in size with advanced histology (15.2%). This would aid patients and physicians to overcome the fear of inappropriately assigning surveillance intervals and encourage the practice of optical resect and discard.[105]

It is important to note that all participating endoscopists in the three studies presented in Chapters 1–3 were trained for optical diagnosis and used IEE technology to facilitate recognition of fine mucosal structures. Similarly, the results of systematic reviews and meta-analyses showed the positive effect of sufficient training in optical diagnosis and using IEE technology such as NBI on the ability of endoscopists to surpass a surveillance interval agreement concordance level of 90% between high-confidence optical diagnosis and histopathology results, as well as a 90% NPV.[40,109] This is in accordance with the results of the DISCARD3 study in the United Kingdom Bowel Cancer Screening Program, in which eight trained endoscopists optically diagnosed 1560 polyps <10 mm in size. It was demonstrated that NBI-assisted optical diagnosis of polyps ≤5 mm in size could provide a surveillance interval agreements of >91% by using either USMSTF, the ESGE, or the British Society of Gastroenterology (BSG) guideline as the reference for assigning surveillance intervals.[110] Likewise, a multi-endoscopists randomized clinical trial demonstrated that trained endoscopists in optical diagnosis could meet the ASGE PIVI criteria with either standard-view or close-view colonoscopies with a non-significant learning curve for optical diagnosis when comparing the first half of the study to the second half.[111] Consistently, a prospective study with 39 qualified endoscopist in optical diagnosis in 13 centers in the Netherlands proved that overall, the participating endoscopists could outperform the recommended criteria for performing both resect and discard and diagnose and leave strategies.[112] Therefore, it can be concluded that resect and discard is an appropriate and feasible paradigm, particularly when adequate training and auditing are integrated into clinical practice.

8.1.1.1 Improving the Safe Implementation of Optical Diagnosis

The ASGE PIVI statement recommends that endoscopists must meet the following thresholds before adopting the two paradigm components of optical diagnosis into real-time practice:

1) For a technology to be used to guide the decision to "leave" suspected rectosigmoid hyperplastic polyps ≤5 mm in place "without resection," the technology should provide a ≥90% negative predictive value (NPV) (when used with high confidence) for adenomatous histology.

2) For colorectal polyps ≤5 mm to be "resected and discarded" without pathologic assessment, endoscopic technology (when used with high confidence) used to determine histology of these polyps, when combined with the histopathologic assessment of polyps larger than 5 mm, should provide ≥90% agreement in assignment of post-polypectomy surveillance intervals when compared with decisions based on pathology assessment of all identified polyps.

Neither the ESGE nor the National Institute for Health and Care Excellence recommend an optical diagnosis quality benchmark.[113,114] Instead, they recommend the use of IEE technologies such as NBI, i-Scan, and FICE, as well as high-definition virtual or dye-based chromoendoscopy equipment to perform optical diagnosis. Moreover, all gastroenterology societies emphasize the importance of auditing and providing feedback to endoscopists regarding their performance to increase the number of high-confidence in vivo histology predictions as a substitute for reference histopathology. Additionally, optical diagnoses should be reported using validated classification systems and adequately documented with photographs.

However, a paradigm shift from excising all diminutive colorectal polyps and evaluating them histologically to "resecting and discarding" or "diagnose-and-leaving" them requires further measures for performing an accurate and reliable in vivo assessment of histology. Some of these requirements are discussed below.

8.1.1.1.1 Standardization of The Management of Diminutive Polyps

It is imperative that gastroenterology initiatives and societies prioritize high-confidence optical diagnosis over histopathology examinations for diminutive polyps and clearly state the risk and benefits associated with optical diagnosis. The criteria for "high confidence" optical diagnosis must be clearly defined. Currently, when a polyp presents endoscopic color, surface and/or vessel features associated with a specific type of histology in the NICE classification with no features associated with another type, a high-confidence diagnosis can be considered.[115] A diagnostic accuracy of ≥90%, and a less than five-second duration for diagnosis have also been proposed as an indication of high confidence histology prediction.[116,117] A further consideration is to stress the relatively low risk of cancer progression in patients with diminutive polyps (even with advanced

villous histology) and the marginal importance of assigning a longer surveillance interval for patients with resected and discarded diminutive polyps. Furthermore, financial incentives should be created for IEE and resect and discard to encourage endoscopists to advocate implementing resect and discard strategy.

8.1.1.1.2 A Learning and Auditing Program

The ASGE PIVI statement emphasizes that only endoscopists who are proficient in using advanced imaging technology should be qualified to perform optical diagnosis.[29] Considering the significant variability of optical diagnosis among individual endoscopists, training programs must focus on enhancing endoscopist proficiency in making a higher number of high-confidence optical diagnoses by educating endoscopists in utilizing ancillary technology, classification systems, and recognizing polyp features for in vivo histology prediction. A standardized and continuous (self/auto) didactic or computer-based training and feedback audit delivers objective benchmarks and insights into the status of optical diagnosis practice and its endorsement in clinical endoscopy and maintains positive endoscopist-based optical diagnosis outcomes for experienced or non-experienced endoscopists.[118,119]. The currently available training modules have not been validated, although they showed promising results in educating endoscopists to make a high-confidence diagnosis.[120-122] A clear example of the significant role of training in improving optical diagnosis is the DISCARD3 study.[110] The DISCARD3 study (explained above) is a follow-up to the DISCARD2 study, in which 28 community-based endoscopists in the United Kingdom could not reach the recommended accuracy for endorsing optical diagnosis in real-time practice.[123] After extensive training and auditing on optical diagnosis, the same endoscopists could easily achieve the ASGE PIVI benchmarks in the DISCARD3 study.

8.1.1.1.3 Validated Optical Diagnosis Classification Systems

A validated and reproducible classification system is valuable to standardize the optical diagnosis among all endoscopists. Several optical polyp histology classification systems are available to distinguish between hyperplastic polyps, adenomas, and sessile serrated polyps (SSPs) based on the fine mucosal characteristics. **Table 1** shows the summary of available classification systems. Some of these classification systems are limited in allowing classification of high-grade vs. low-grade dysplasia and/or SSA from SSPs. The NICE classification system is the most clinically relevant and accepted classification system among endoscopists to distinguish hyperplastic, adenomas and cancer from each other.[116] However, it lacks the diagnostic criteria for diagnosing

SSP/As and must be supplemented by another classification system. The WASP classification system can differentiate adenomas from SSPs if a polyp possesses two of the following characteristics: clouded surface, indistinctive border, irregular shape, and dark spot inside crypts. The diagnostic accuracy of the WASP classification for high-confidence diagnosis of SSPs could reach 91% (95% CI=88-94), thus making it a valid alternative to the NICE classification system.[124] The results of the study in Chapter 2 showed that the WASP classification could not reach the benchmarks and needs further improvement. The SIMPLE classification system also uses the surface and vascular pattern as well as the irregular/indistinctive lesion border to distinguish between hyperplastic, adenomatous and sessile serrated polyps.[125] In a validation study, this system achieved 94% (95% CI=89-97) accuracy, with almost a third of the included polyps being SSPs, indicating its high performance in distinguishing SSPs from hyperplastic polyps and adenomas.[125] The Hiroshima classification system has been established based on characterizing microvasculature and pit pattern in order to distinguish between hyperplastic polyps, tubular adenomas and carcinoma.[126] This classification can distinguish hyperplastic polyps (type A) from carcinomas (type C3) with a high accuracy but it does not reliably discriminate type B, C1 and C2 subtypes.[127,128] Moreover, the Japan NBI Expert Team (JNET) classification system must be used only for distinguishing type 1, 2A and 3 from each other but not for diagnosing type 2B polyps.[129,130] Also, the Sano classification is a good alternative showing an excellent performance for diagnosing only type I and II classifications or distinguishing neoplastic from non-neoplastic polyps.[131-133] Noteworthy, the findings of the article in **Chapter 2** highlight the persistent inability of optical diagnosis for predicting SS histology subtype despite research efforts to develop specific classification systems. In contrast to using the WASP classification system, optical diagnosis using either NICE or Sano classifications could reach the recommended ASGE PIVI benchmark.[26]

Table 1 Summary of optical diagnosis classification systems.

Classification system	**Development year**	**Imaging technique used**	**Diagnostic criteria**	**Strength/Limitation**
SIMPLE[125]	2018	i-Scan, NBI	Surface and vascular pattern, lesion border: Hyperplastic, adenoma, SSP/A	- Strength: high accuracy for diagnosing SSPs; can be used with i-Scan; NPV reached 91%;

Classification system	Development year	Imaging technique used	Diagnostic criteria	Strength/Limitation
				- Limitation: does not distinguish villous elements or the grade of dysplasia within adenomas
BASIC[134]	2018	Blue light	Polyp Surface, Pit Appearance, Vessels Pattern: hyperplastic polyps, adenomas, and neoplasia	- Limitations: does not provide criteria for the diagnosis of SSPs; limited validation studies; does not distinguish villous elements or the grade of dysplasia within adenomas
WASP[124]	2016	NBI	based on pre-existing NICE classification criteria: Hyperplastic, adenoma, SSP/A	- Strength: high accuracy for diagnosing SSPs; does not distinguish villous elements or the grade of dysplasia within adenomas
JNET[135]	2016	High-magnification NBI	based on the previously developed NICE classification: Type 1 (Hyperplastic polyp/ SSP), Type2A (Low grade intramucosal neoplasia), Type 2B (High grade intramucosal neoplasia/ Shallow submucosal invasive cancer), Type 3 (Deep submucosal invasive cancer)	- Limitation: does not provide criteria for the diagnosis of SSPs; does not distinguish type 2B
NICE[116]	2012	NBI	color and vascular and surface patterns: Type 1 (hyperplastic and sessile serrated lesions), Type 2 (adenoma); type 3 (deep	- Limitations: poorly adapted to use with FICE imaging; does not provide criteria for the diagnosis of SSPs; does not distinguish villous elements or the grade of dysplasia within adenomas

Classification system	Development year	Imaging technique used	Diagnostic criteria	Strength/Limitation
			submucosal invasive cancer)	
Hiroshima[126]	2009	NBI	microvasculature and pit pattern: type A (hyperplastic polyps), type B (tubular adenoma), type C (carcinoma)	- Strength: high accuracy for diagnosing type A from C3 subtype, and C2 - Limitations: does not provide criteria for the diagnosis of SSPs; low accuracy for diagnosing types B, C1, and C2 subtypes; does not distinguish villous elements or the grade of dysplasia within adenomas
SANO[136]	2006	NBI	based on the previously developed KUDO classification of pit pattern: type I (hyperplastic polyps), type II (adenomas), type III (carcinoma)	- Limitations: does not provide criteria for the diagnosis of SSPs; does distinguish villous elements or the grade of dysplasia within adenomas

NICE: NBI International Colorectal Endoscopic; SSA: sessile serrated adenoma; SSP: sessile serrated polyp; NBI: narrow-band imaging; WASP: Workgroup on serrAted polypS and Polyposis; JNET: Japan NBI Expert Team

8.1.1.1.4 The Use of Image-enhanced Endoscopy

Several IEE technologies are available to help endoscopists achieve a higher accuracy in in vivo optical histology classifications.[137] For the purpose of this thesis, several chromoendoscopy techniques were used to increase the detection of polyps during colonoscopies.[138-140] The classic chromoendoscopy involves application of a contrast dye, indigo-carmine or methylene blue to enhance the topography and microtopography of the colonic mucosa and improve the visualization of flat diminutive polyps. The conjoint detection benefit of high-definition and chromoendoscopy has been shown in a clinical trial by Kahi et al, where a higher number of flat or diminutive adenomas were detected using high-definition chromoendoscopy than white-light endoscopy.[141] A significant benefit of chromoendoscopy is the increased detection of proximal

serrated lesions, which are associated with a higher risk of PCCRC if failed to be detected.[9,76,142] The virtual chromoendoscopy has been currently integrated in high-definition endoscopes, which are associated with a higher number of detected polyps and adenomas, especially flat adenomas, compared with standard white-light endoscopes.[143,144] During a virtual chromoendoscopy, a light filtering (NBI, Olympus Tokyo Japan), narrow wavelength laser (BLI/LCI Fujifilm, Tokyo, Japan) or post-image acquisition processing (I-Scan Pentax, FICE Fujifilm, Tokyo, Japan) will be emitted from or provided by a high-definition endoscope to imitate enhanced surface contrast and microtopography provided by the classic chromoendoscopy.[137] NBI involves three optical filters to filter out red light wavelength, leaving only narrow bandwidth that can penetrate colon mucosa less deeply and enhance mucosal structure.[137,145,146] The effect of NBI on ADR is controversial in the literature. A meta-analysis of 11 randomized clinical trials comprising 4491 patients and 6636 polyps found that NBI could significantly increase ADR by 14% compared to high-definition white-light endoscopy, with up to 30% increase in ADR when the second-generation bright NBI was used.[147] The non-ADR and flat ADR was also increased with NBI compared with white-light endoscopy (ORs=1.24).[147] In another clinical trial, NBI could increased the detection of SSPs to more than two-folds (SSL detection rate: RR=2.04; 95% CI=1.18-3.54).[148] In contrast to these findings, a randomized clinical trial of 330 patients showed no significant accuracy, sensitivity and NPV for histology prediction of polyps <10 mm in size using NBI compared with white-light colonoscopy.[149] Similarly, a prospective study of 147 patients found a slight superior but non-significant sensitivity and PPV for optical diagnosis of polyps <10 mm in size using high-definition NBI colonoscopy over white-light colonoscopy.[150] Nonetheless, NBI remains as an important tool for optical histology diagnosis given that the optical histology classification systems are based on NBI. The i-Scan IEE technology (Pentax, Tokyo, Japan) is another virtual chromoendoscopy tool that provides an enhanced surface, contrast and tone to display mucosal characteristics by using limited red, green and blue bandwidth light. Recent studies showed the superiority of high-definition i-Scan colonoscopy over high-definition white-light colonoscopy for adenoma and flat adenoma detection.[151,152] A recent randomized clinical trial conducted tandem colonoscopies in 740 patients and found i-Scan resulted in a significantly higher ADR than high-definition white-light colonoscopy (47.2% vs 37.7%; p-value=0.01).[153] Another randomized clinical trial compromising 61 patients with Lynch syndrome found that the adenoma miss rate was more than two times higher in high-definition white-light colonoscopy vs. i-Scan colonoscopy. However, no difference in ADR was detected between i-Scan and high-

definition white-light colonoscopy.[154] Moreover, Optivista i-Scan optical enhancement (Pentax, Tokyo, Japan) improves i-Scan post-processing images by filtering the light to closely match hemoglobin wavelength emission patterns, improving accuracy of optical histology predictions by increasing contract between mucosal and vascular patterns. A prospective study used Optivista optical enhancement combined with NICE classification system and showed that this system could reach a high accuracy (91%) and NPV (94%), surpassing the ASGE PIVI recommended threshold.[155]

Additionally, in the studies included in **Chapter 1–3**, the use of near-focus view was allowed for a higher image magnification to increase the chance of accurate optical diagnosis. The VALID multicenter randomized clinical trial determined that it was more likely to result in a higher number of high-confidence optical diagnosis with near focus view compared with the standard view when during colonoscopies using NBI (85.1% vs. 74.5%, OR=2.2; 95% CI=1.6-3.0, p<0.0001).[156] Moreover, the endoscopists were able to reach a higher NPV and surveillance concordance when near focus was used.[156]

CADx systems are the most promising add-on devices, which are developed to empower endoscopists to perform optical diagnosis (discussed in **Chapter 6**). The emergence of new advances in machine learning technology, such as deep learning, have enabled computer-based systems to process colonoscopy images and videos and support endoscopists in real-time to decide on the most-probable histology with high confidence. Given that there is a correlation between operator expertise and the ability to meet recommended ASGE PIVI benchmarks[40], CADx models may help standardize and automate optical diagnosis, so that all endoscopists, regardless of their expertise, are capable of effectively managing diminutive polyps. The high diagnostic performance of these systems would reinforce the practice of optical diagnosis in daily practice.[157] Most available CADx systems have been trained and validated based on unaltered images or video frames derived from NBI colonoscopy videos and can efficiently differentiate hyperplastic and neoplastic polyps using polyp features in the NICE classification systems.[92,158] However, a recent research targeted the development of CADx platforms using data derived from standard colonoscopies without using IEE technologies[159], which could successfully enable the implementation of both diagnose and leave and resect and discard strategies in 82% and 39% of diminutive polyps, respectively.[159] This model could allow for leaving diminutive colorectal polyps in situ by exceeding the recommended NPV benchmark of at least 90% (97.6%), which was even

higher than the NPV (96.5%) achieved by endocystoscopy (available mostly in Asian countries).[101] Additionally, the agreement between CADx and pathology-based surveillance interval recommendations was 95.6% using the ESGE and 95.9% using the ASGE guidelines. Similar to other reported CADx models[101], the accuracy of this model for the optical diagnosis of proximal diminutive polyps is still lower than distal diminutive polyps regardless of the use of magnifying or white-light colonoscopy, indicating the possibility of a weaker correlation between histology and available features for in vivo histology classification, which may hamper the proximal polyp optical diagnosis especially for non-expert endoscopists. Therefore, it can be concluded that the new generation of CADx systems can obviate the need for IEE technology for detecting fine mucosal and vasculature architecture, making it more accessible by avoiding the procurement of additional equipment for the standard endoscopy workstation.[49,114]

8.1.2 Improving Resect and Discard Strategy Using Non-Optical Approaches

In **Chapters 2 and 3**, two non-optical models were proposed as the potential paths forward to resect and discard strategy and clinical management of patients with detected diminutive polyps.

The LBRD would enhance the safety of resect and discard practice by reducing the risk of assigning long surveillance intervals. Further, it could outperform the recommended ASGE PIVI benchmark and optical diagnosis for assigning surveillance intervals against the reference of pathology.[26,160] The PBRD approach bears a close resemblance to the LBRD approach by offering a safe alternative to optical diagnosis. The agreements between the surveillance intervals using either PBRD model (calculated post-hoc) or optical diagnosis and pathology could reach the ASGE PIVI benchmark.[26] This agreement was significantly higher for PBRD strategy compared to optical diagnosis (98% vs. 95.8%; p-value=0.005). Both LBRD and PBRD models as well as optical diagnosis contributed to significant reductions in required histopathology evaluations and increased the percentage of patients with same-day surveillance interval assignment.

The non-optical approaches hold several advantages over optical diagnosis. First, they mitigate the need for special training and auditing to interpret the histological features of polyps and to memorize complicated optical histology classification systems (e.g., NICE or WASP classifications). Noteworthy, a formal training and auditing program for optical diagnosis is not available in most academic and community-based endoscopy centers in North America and

Canada. As a result, there is uncertainty regarding the feasibility of optical approaches in most centers, especially for unexperienced trainees or specialists. Second, non-optical diagnoses are based on the size, number, and location of the polyps, which are routinely reported in all endoscopic reports. Third, they follow the same principles as those taken into account by the USMSTF guideline (i.e., a positive first-degree family history of colorectal cancer or inadequate bowel preparation) for adjusting the recommendation of the next surveillance plan for individual patient. Fourth, the implementation of non-optical models does not rely on auxiliary IEE technology that can enhance the accuracy of the detection of polyp features. These non-optical models can provide significant cost and time savings alternatives to promote the resect and discard strategy in developing countries or community-based centers with limited access to IEE, as well as in areas where endoscopists have not yet achieved the recommended benchmarks for a safe practice of optical diagnosis.

Some limitations may hinder the use of non-optical approaches that must be addressed in future research:

First, none of proposed LBRD and PBRD strategies as well as optical diagnosis could reach the recommended NPV threshold of 90% for “diagnosing and leaving” rectosigmoid diminutive polyps in situ during real-time colonoscopies. These findings refute the results of a systematic review and meta-analysis by the ASGE Technology Committee, which reported that the recommended NPV ≥90% can be reached easily especially by expert endoscopists, in academic centers, and if it is assisted by electronic chromoendoscopy technology, particularly NBI.[40] In fact, given that 85% of diminutive rectosigmoid polyps are non-adenomatous seldom harboring advanced histological features (villous features or high-grade dysplasia) and very rarely cancer, the “diagnose and leave” approach is currently endorsed by most of experienced endoscopists as a safe practice for managing diminutive rectosigmoid polyps.[102]

Second, the surveillance intervals assigned based on the PBRD model used by the endoscopists immediately after colonoscopy could not reach the recommended benchmark, implying the suboptimal adherence of endoscopists to PBRD criteria. It may be due to the relatively difficult criteria of the PBRD approach and inadequate integration of patient’s clinical profile into the design of this approach, such as second-degree family history of CRC or other individual factors. Nonetheless, a significant learning curve was observed for employing the PBRD model accurately

with study progression, suggesting that it may be a safe alternative to optical resect and discard strategy pending further research confirming its effectiveness in real-time endoscopic practice.

Third, although the LBRD strategy could potentially be used in developing countries, it has been debated that it is less likely to be adopted in routine clinical practice in North America.[24] The assignment of surveillance intervals using this model was based on the high end of the surveillance interval range recommended by the USMSTF in 2020.[62] The USMSTF recommend a surveillance interval of 7–10 years for patients with one or two detected diminutive low-risk adenomas (i.e., conventional adenomas without having advanced histological features), and 5–10 years for patients with three or four detected diminutive low-risk adenomas. Considering the non-adherence of North American endoscopists to optical diagnosis and their desire toward repeating endoscopies in shorter intervals, further research might be required to add clarifications to the accuracy of the LBRD strategy based on the American practice pattern (i.e., assigning 7 years instead of 10 years of surveillance interval to a patient with 1–2 diminutive adenoma(s), and 3 years instead of 5 years surveillance interval to a patient with 3–4 diminutive adenomas).

8.2. Computer-based Measurement of Polyp Size

8.2.1 The Importance of Accurate Estimation of Polyp Size

In PCCRC prevention, accurate polyp size measurement is pivotal to advising on an appropriate post-polypectomy patient management. According to the latest USMSTF guideline, surveillance intervals should be based on the number, histology, and size of polyps detected during a colonoscopy.[62] However, one major criterion for assigning surveillance intervals is the cut-off size of 10 mm for a polyp, regardless of the histology. For instance, a patient with a detected large (≥10 mm) polyp must be re-examined within three years after the index colonoscopy regardless of polyp histology, while a patient with a 9 mm conventional adenoma must be re-examined after 7–10 years. Moreover, besides the impact of endoscopists' expertise on polypectomy, a complete resection of detected polyps partly depends on an accurate choice of polypectomy tool or technique. **Table 2** summarizes the most recent recommended polypectomy techniques by the most recent U.S. and European guidelines.[63,65]

Table 2 Recommended polypectomy techniques for polyps of different sizes.

Guideline	Polyp size	Recommendations
ESGE[65]	Diminutive polyps (≤ 5mm in size)	Cold snare
	Sessile polyps 6–9mm in size	Cold snare
	Sessile polyps 10–19 mm in size	Hot snare
	Pedunculated polyps of any size	Hot snare with the injection of dilute adrenaline and/or mechanical hemostasis to prevent bleeding in polyps with head ≥ 20 mm or a stalk ≥ 10 mm in size
	Polyps of any size without suspicion of superficial invasive carcinoma (except rectosigmoid)	EMR, ESD, and standard snare polypectomy attempted en-bloc
	Polyps of any size with suspicion of superficial invasive carcinoma (except rectosigmoid)	EMR, standard snare polypectomy attempted en-bloc; otherwise, ESD attempted en-bloc
	Non-invasive polyps 10–19 mm in size	Hot snare polypectomy with or without submucosal injection
	Polyps 10–19 mm in size with suspected superficial submucosal invasion	EMR, ESD
	Laterally spreading and sessile colorectal lesions <20 mm in size or lesions located in difficult sites such as the ileocecal valve, appendiceal orifice, anorectal junction, behind haustral folds, or lesions ≤ 25 mm in size in the rectum	EMR attempted en-bloc
	Laterally spreading and sessile colorectal lesions ≥20 mm in size	ESD attempted en-bloc (equivocal with surgery, except for rectal lesions)

	or lesions in the rectosigmoid with high suspicious of invasive carcinoma and poor prognostic factors	
	Large polyps with advanced endoscopic imaging characteristics of deep submucosal invasion with/without lymphovascular involvement	Surgery
USMSTF[63]	Diminutive (≤5 mm in size) and small (6-9 mm in size) lesions	Cold snare
	Pedunculated lesions 10 mm	Hot snare with prophylactic mechanical ligation of the stalk with a detachable loop or clips on pedunculated lesions with head 20 mm or with stalk thickness 5 mm to reduce immediate and delayed post-polypectomy bleeding
	Non-pedunculated lesions 10–19 mm in size	Cold or hot snare polypectomy (with or without submucosal injection)
	Non-pedunculated lesions ≥20 mm in size	EMR

EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection

Furthermore, polyp size correlates with the risk of malignancy and thus, would impact the decision-making upon the treatment options.[25] Moreover, the safe implementation of optical polyp diagnosis depends on the differentiation of diminutive from small polyps. This is particularly more important for measuring polyps 1–3 mm in size regarding the unreliability of histopathology for histology determination of polyps in this size range and the higher concordance between AI-assisted histology prediction and high-confidence optical diagnosis over histopathology outcomes.[93]

The body of literature consistently reports a great interobserver variability among endoscopists and pathologists for size measurement, which potentially could affect the decision-making upon the safe clinical descion-making.[161,162] These findings further highlight the importance of standardizing polyp size estimation in clinical practice.

A major obstacle to validating and standardizing the practice of size measurement is the lack of a "gold standard." Most research relies on pathologic measurement of polyp specimens to validate adjunctive measurement techniques due to reproducibility and the absence of perception error or rater preference. However, several factors may lead to under or overestimation of size or hamper pathologic size estimation. These factors include: polyp specimen shrinkage due to coagulation or fixation in formalin, misinterpretation of healthy resection margin as a part of polyp tissue, piecemeal resections, damaged or crushed and lost specimens during retrieval.[163] **Chapter 4** discussed the available technology for improving the accuracy of endoscopic polyp size measurements. None of these methods could overcome human perception errors and reach a similar consistent high accuracy among all endoscopists regardless of their expertise.

8.2.2 Assessing the Clinical Feasibility of Using a Virtual Scale Endoscope for Measuring Polyp Size

In **Chapter 5**, the clinical feasibility of the application of a new state-of-art virtual scale function for an endoscope (VSE; SCALE EYE) was evaluated through a pilot study.[164] Before this clinical evaluation, two proof-of-concept, ex-vivo blinded randomized clinical trials were conducted to evaluate the feasibility and accuracy of VSE using artificial polyps (manuscripts submitted, awaiting final decisions). The artificial polyps were created in different sizes and morphologies and measured using a Vernier caliper to obtain a reference of measurement. The findings of both studies underscore the higher performance of VSE compared to visual estimation of polyp size, or other measurement tools (i.e., biopsy forceps, Napoleon endoscopic ruler). Nevertheless, similar to other research studies, there was a wide variation in polyp measurements among endoscopists. In the first study, three trainees and three staff gastroenterologists performed 60 measurements randomized at a 1:1:1 ratio using VSE, biopsy forceps, and Napoleon endoscopic ruler (a total of 30 measurements; 120 measurements by each method) (**Figure 1**).

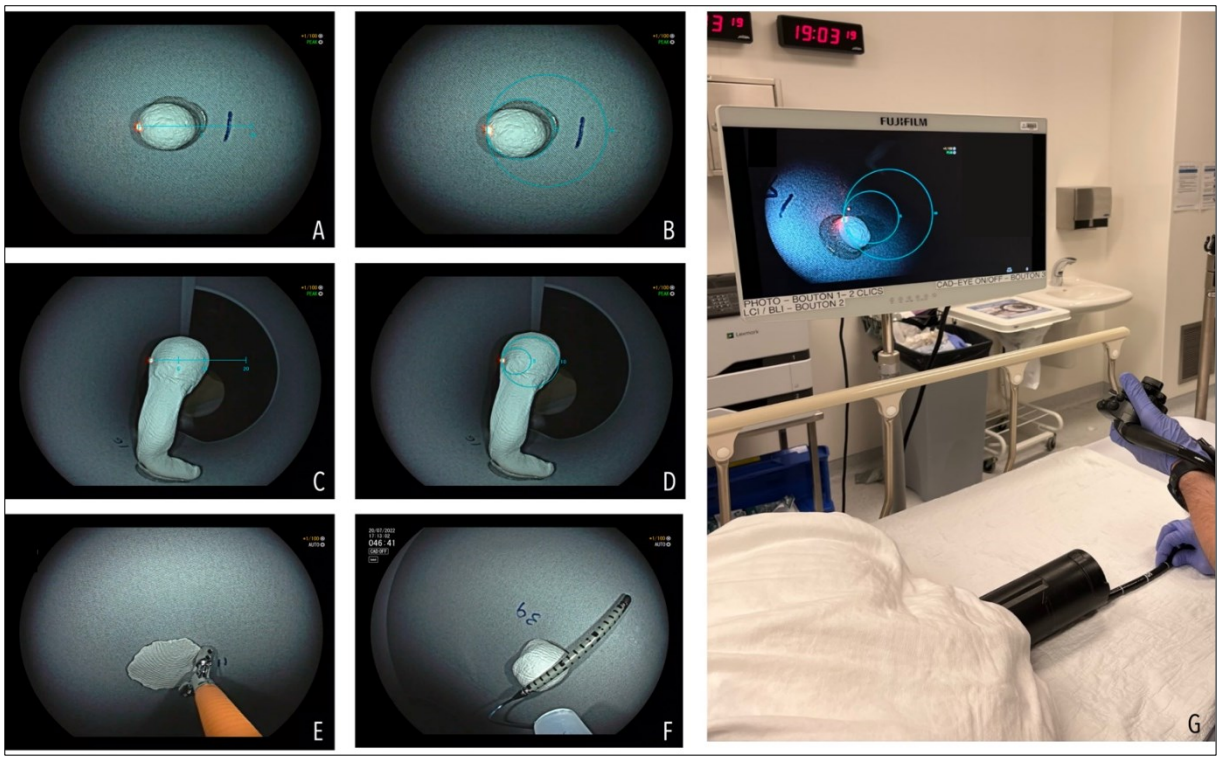
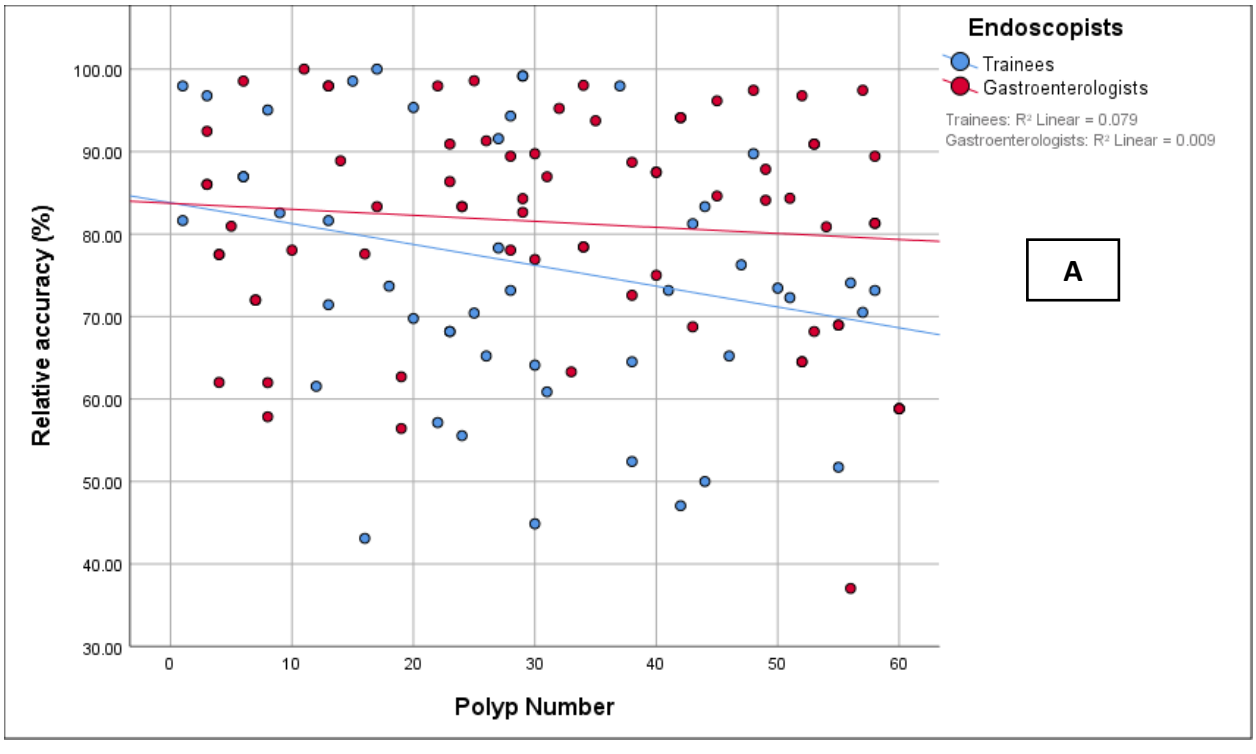
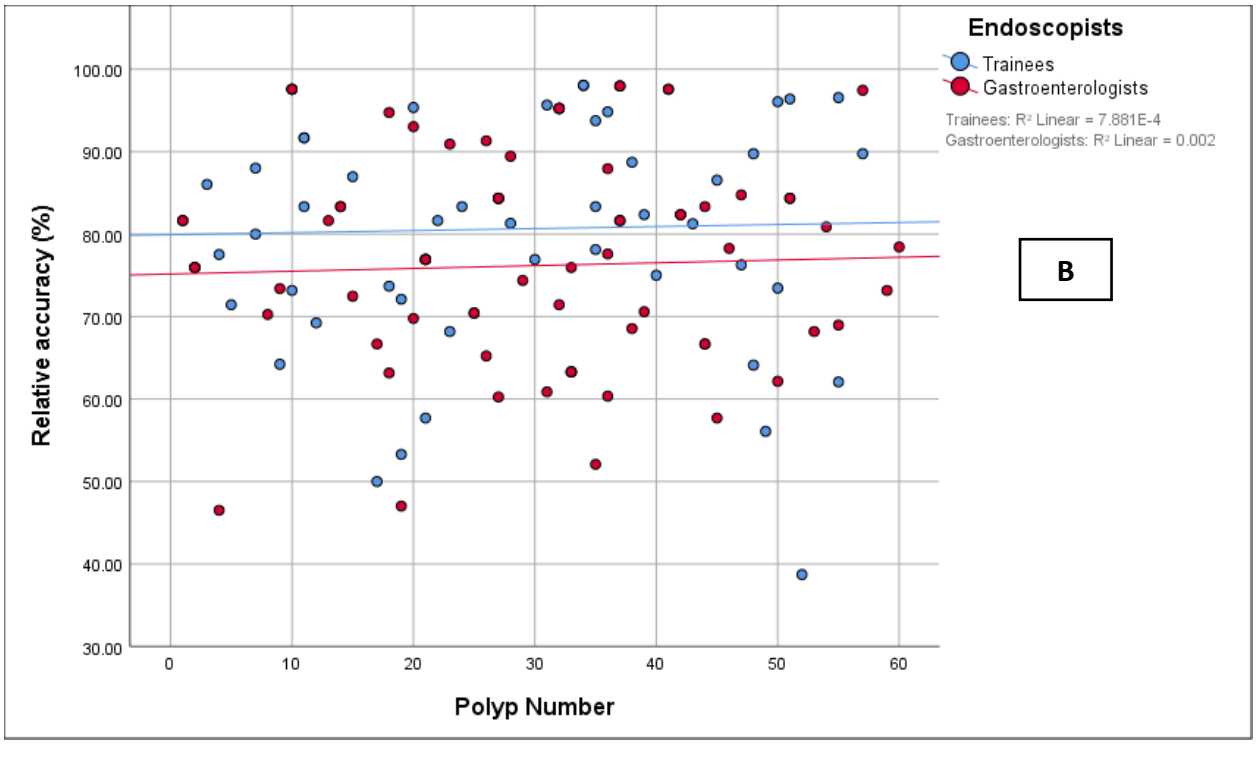


Figure 1 (A) Polyp size estimation using the visual scale endoscope with linear scale (B) Polyp size estimation using the visual scale endoscope with circular scale (C) Pedunculated polyp size estimation using the visual scale endoscope with linear scale (D) Pedunculated polyp size estimation using the visual scale endoscope with circular scale (E) Polyp size estimation using forceps (F) Polyp size estimation using Napoleon endoscopic ruler (G) Virtual scale projected on a live endoscopy screen during conduction of the study. Derived from: Djinbachian et al. (2022). Comparing size measurement of simulated colorectal polyps when using a novel virtual scale endoscope, endoscopic ruler or forceps: A blinded randomized trial. Submitted awaiting final decision. Image courtesy of Dr. Daniel von Renteln with permission from Dr. Roupen Djinbachian.

No significant difference was observed for measurement duration by all methods. VSE had a significantly higher relative accuracy (82.7%; 95% CI=80.8–84.8) than biopsy forceps (78.9%; 95% CI=76.2–81.5) and Napoleon ruler (78.4%; 95% CI=76.0–80.8). Generally, trainees had similar relative accuracies compared to expert endoscopists using all three methods (**Figure 2**). However, they showed a lower accuracy of measurement with biopsy forceps that reduced over the course of measurements. This can be explained by the relatively technical difficulty in estimating polyp sizes using biopsy forceps and fatigue playing a greater role in the accuracy of measurements by trainees. In contrast, trainees had higher relative accuracies with Napoleon endoscopic ruler and

VSE than expert endoscopists. A learning curve was observed for expert endoscopists over time, indicating they could reach the accuracy of trainees by the end of study.





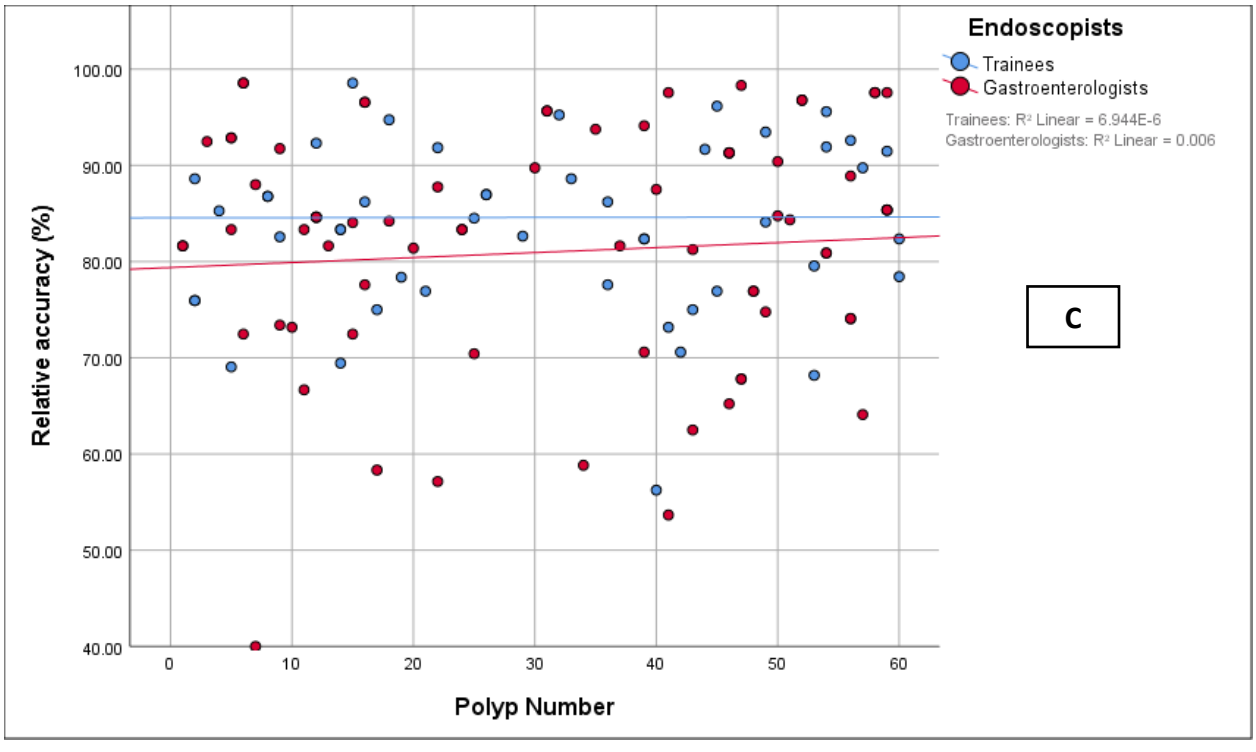


Figure 2 A. scatter plot of the distribution of the relative accuracies of measurement with biopsy forceps for trainees and gastroenterologists; B. scatter plot of the distribution of the relative accuracies of measurement with Napoleon ruler for trainees and gastroenterologists; C. scatter plot of the distribution of the relative accuracies of measurement with virtual scale for trainees and gastroenterologists. Image courtesy of Dr. Daniel von Renteln with permission from Dr. Roupen Djinbachian.

The interobserver agreements across all categories of measurement methods was more than 93% among all endoscopists or three trainees and three staff gastroenterologists. Interestingly, biopsy forceps and Napoleon ruler did not misclassify polyps ≤5mm as >5mm, but VSE misclassified 4.2% of polyps ≤5mm as >5mm. Moreover, 25.6%, 25.5%, and 22.5% of polyps ≥10mm were misclassified as <10mm with Napoleon ruler, biopsy forceps, and VSE, respectively. No polyp <10mm were misclassified as ≥10mm with Napoleon ruler whereas 5.5% and 7.1% polyps were misclassified with biopsy forceps and VSE, respectively. All methods misclassified a high percentage of polyps ≥20mm as <20mm; however, VSE misclassified a lower percentage of these polyps (8.3%) compared with biopsy forceps and Napoleon ruler (66.7%, 75.0%, respectively). This indicated a higher performance of VSE compared to other methods especially

for polyps at the size cut-off of 20 mm. Noteworthy, the difference between the misclassification by methods (One-way ANOVA) was significant for misclassifying polyps ≥20mm as <20mm in size.

In the second study, 60 simulated polyps across four different size groups (0–4.9 mm, 5–9.9 mm, 10–19.9 mm and ≥ 20 mm) and three different Paris morphology groups (flat, sessile and pedunculated) were measured by three staff gastroenterologists and three trainees (a total of 359 measurements; one polyp broke during the last measurement) using random allocation of either visual assessment or VSE. VSE showed significantly higher relative accuracies compared with visual assessment of size across the groups of polyps sized ≥5 mm. The relative accuracy of VSE was also higher than visual assessment of size among diminutive polyps, but this estimation did not reach statistical significance. It was also determined that VSE could measure the size of sessile and pedunculated polyps with a higher accuracy compared to the visual assessment of size. Additionally, VSE misclassified a lower percentage of ≥ 5 mm polyps as < 5 mm (2.9%), ≥ 10 mm polyps as < 10 mm (5.5%) and ≥ 20 mm polyps as < 20 mm (21.7%) compared to visual estimation (11.2; 24.7 and 52.3% respectively; p=0.008, p<0.001 and p=0.003).

The results of these two studies alongside the in vivo pilot study highlight the effectiveness of VSE in accurately measuring polyp size during real-time colonoscopies. The routine use of polyp measurement using VSE technology might help endoscopists choose adequate polypectomy techniques and assign appropriate surveillance intervals. In addition, it would allow future studies to integrate objective size measurements when evaluating the prevalence of certain pathologies in colorectal polyps or outcomes associated with polypectomy techniques. Moreover, VSE can be used as a tool to capture ground truth information datasets to develop future AI-assisted systems with an integrated automated measurement module. Further research including a higher sample of larger polyps is required to draw a conclusion on the efficiency of the VSE for measuring larger polyp size.

8.3. Recent Advances in Computer-based Colonoscopy

8.3.1 The Barriers of Application of Computer-based Systems

Although colonoscopy is the most cost-effective tool for preventing CRC through detecting and removing cancer precursor lesions, its potential for preventing CRC and its associated mortality

is limited by the high level of operator dependence.[165] Quality is a subjective concept; thus, several societies and initiatives have attempted to standardize colonoscopy quality by establishing easy-to-be-measured quality metrics.[29,78,166] The most clinically relevant quality metric is ADR, which is inversely related to the risk of PCCRC.[78] Endoscopists can partially improve their skills in detecting and histologically classifying polyps, but may encounter challenges in achieving the recommended standards or miss reporting them. Various colonoscopic techniques (e.g., changing patient position or pressure on abdomen during withdrawal, dye-based chromoendoscopy) and ancillary advanced imaging modalities (e.g., high-definition endoscopes, IEE such as virtual chromoendoscopy) have been developed to enhance ADR, effective management of insignificant diminutive polyps, and reduce PCCRC risks.

There is no doubt that CADe and CADx systems hold the greatest promise as adjunctive tools for improving polyp detection, classification and colonoscopy quality assessment in preventing PCCRC. The CADe systems have been shown to significantly increase ADR up to 11% through clinical trials using ADR as the primary quality metric.[167] Moreover, CADx systems could facilitate the management of diminutive polyps by offering the highest diagnostic performance for in vivo differentiating hyperplastic from neoplastic polyps. However, the broad application of CADe platforms is limited by several methodological issues, and some reservations remain regarding the value of these systems. First, the detection potential of CADe systems is routinely assessed in clinical trials using ADR as the primary endpoint. This is driven by the fact that ADR is the prime surrogate measure of colonoscopy quality. However, the value of ADR in the population of symptomatic patients is poorly established. Second, AI-assisted colonoscopy highly relies on the endoscopist's ability to visualize colon specifically during loop formation, with angulated and/or narrowed sigmoid colon, or redundant colon[168], since CADe is only capable of detecting adenomas on exposed mucosa. Therefore, increasing ADR through AI-empowered systems may not necessarily translate into a decrease in the incidence and mortality of PCCRC in the screening population. Third, most researchers use data derived from a single source (e.g., colonoscopies performed at a single facility) to train and validate AI models. An overlap between datasets would lead to "model overfitting" and potentially erroneous interpretation of the model hyperparameters.[169] Fourth, the trials of evaluating CADe were conducted at mother institutes under controlled and recognized conditions, using data similar to that used for the development of the model. As a result, the generalization of similar remarkable findings in another colonoscopy setting may be hindered due to the possibility of inducing Hawthorne effect, overfitting and

overestimating the effectiveness of the AI model.[167,170] Finally, a lack of reliable and annotated ground truth (i.e., big data) would negatively impact model performance. These problems can be addressed by developing large-scale multi-centre trial platforms for evaluating AI systems as part of national screening programs that provide heterogeneous and extensive data sources collected from patients with a range of race, age, sex, and anatomical characteristics, and by endoscopists with various expertise level. Consequently, it is possible to conduct interim analyses, make an early decision regarding the effectiveness of a model, and correct errors at the early stages of data collection to ensure optimized model performance in various settings.[77,170,171]

8.3.2 The Importance of Detecting Cecal Anatomical Landmarks

A high-quality colonoscopy involves careful visualization of the entire colonic mucosa, from the anus to the cecum, as well as the detection, classification, and removal of cancer precursor lesions, if necessary.[78,172] This can be accomplished primarily by identifying the ICV, OA, and intubating the cecum. The ASGE and ESGE recommend the cecal intubation rate (CIR) of ≥90% and ≥95%, respectively, in all or only screening colonoscopies.[78,173] Cecal intubation must be intended in all procedures to ensure the complete inspection of the right colon, especially the medial wall of the cecum between the ileocecal valve and appendiceal orifice. Additionally, high-quality endoscopic photos of the detected AO with the cecal strap fold visible around the appendix and the cecum distal to the ICV with the lips of the ICV visible must be included in the colonoscopy report as evidence of a complete procedure.[78] However, the anatomical variation in cecal structures may influence the quality of the obtained photos.[174] If the photo-documentation of the cecal landmarks is not possible, the terminal ileum must be intubated, and the small bowel villi, circular valvulae connivente, and lymphoid hyperplasia must be documented. Cecal intubation significantly depends on the skills of the individual endoscopists but can be facilitated by using variable-stiffness endoscopes, pediatric endoscopes, or magnetic endoscopic imaging to visualize the scope configuration in real-time.[174-188] A major benefit of cecal intubation is associated with an increased likelihood of detecting sessile serrated and flat lesions, particularly in the right colon, where they are more difficult to detect.[78] Subsequently, an increased CIR is inversely related to the rate of proximal PCCRC.[81] A related study found that patients whose endoscopies were performed by endoscopists with a higher completion rate of colonoscopy would be less likely to develop PCCRC.[81] It can be explained by the correlation between poor cecal

intubation and low ADR and high adenoma miss rate. Therefore, aborted colonoscopies with inadequate bowel preparation or those with polypectomy or stricture treatment must not be counted in the calculation of the cecal intubation rate.

8.3.2.1 Previous Research Addressing the Detection of Cecal Anatomical Landmarks

The complete detection and precise classification of polyps, as well as accurate detection of cecal landmarks as an indication of a complete procedure, are beyond the power of the human eye and might be fallacious, rendering an increased risk of PCCRC. Despite the importance of achieving a complete colonoscopy, there is no auditing system that can ensure colonoscopy quality and completeness. Due to the significant impact of bowel preparation and endoscopist fatigue on successful cecal intubation, the use of AI for detecting key anatomical landmarks during real-time colonoscopy is highly beneficial. The development of AI models for detecting cecal landmarks has received relatively insufficient research effort. Few studies have evaluated the ability of AI to precisely and automatically assess the quality of a colonoscopy procedure, including identifying important anatomical landmarks and withdrawal time, especially when the endoscopic field is blurry. [95,189-191] These studies have the following major drawbacks: a small sample size, low ADR, lack of testing in an independent dataset, confusing alarm system, and never exceeding a prototype. One initial research used the K-mean classifier technique to automatically classify the obtained images into either appendix image class or non-appendix image class.[192] Using the features representing the likelihood of no colon lumen, the ratio of edge pixels belonging to curvilinear structures, and partial ellipses in an appendix image, 800 manually-annotated images derived from five colonoscopies were examined by this model. Although the model accuracy for classifying appendix images was promising (90%), the exclusion of the images containing tangential AO as well as a relatively high false positive classification rate precluded further clinical application of the model. Likewise, Wang et al used two algorithms to automatically detect AO. The first algorithm used geometric shape, saturation and intensity changes along the norm direction (cross-section) of an edge to discriminate images containing AO from other images.[95] In the second algorithm, frame intensity histograms were used to detect a near-camera pause during AO inspection in order to identify videos that contained an appendix. The average sensitivity and specificity of the first algorithm was 96.86% and 90.47%, respectively. The average accuracy of the second algorithm for detecting appendix videos was 91.30%. However, this study used only 23 colonoscopy videos, which limits its generalizability. Recent advances in AI and deep learning have led to a growing consensus on the possibility of automatic

detection of a complete colonoscopy. An AI model using CNN algorithm was developed using 3,222 images (6,663 containing AO and 1,322 non-AO) extracted from 35 colonoscopy videos to detect the AO irrespective of bowel preparation.[193] The accuracy and the area under the receiver operating curve of this model was 94% and 98%, respectively, for classifying AO and non-AO images. This model had a relatively high performance but has never been tested in practice. Another CNN model was trained using 6,487 colon images prospectively obtained from over 300 colonoscopy procedures and annotated by two expert endoscopists for anatomic landmarks, lesions, and bowel preparation adequacy.[194] This model intended to automatically calculate CIR and withdrawal time. When all images (probably including unprocessed and suboptimal-quality images) were used to train the CNN model, the model accuracy was 88%. However, when the model was trained using a subset of 1000 optimal images, the accuracy and the under the receiver operating characteristic of the model were 98% and 99%, respectively. This model has not yet been tested in a real-time colonoscopy procedure, so its effectiveness remains unknown. Furthermore, Li et al. developed several image-based and video-based CNN models to calculate withdrawal from the moment the ICV is detected.[195] This exploration resulted in the highest accuracy of 99.6% using an image-based dataset. However, the model only achieved a 70% accuracy when a video-based dataset was used.

8.3.3 Developing A Deep-learning Model for The Automatic Detection of Cecal Landmarks and Their Discrimination from Polyps and Normal Mucosa

The proposed AI module in **Chapter 7** is based on a CNN algorithm to distinguish the AO, ICV, polyp and normal mucosa from each other (**Figure 3**).

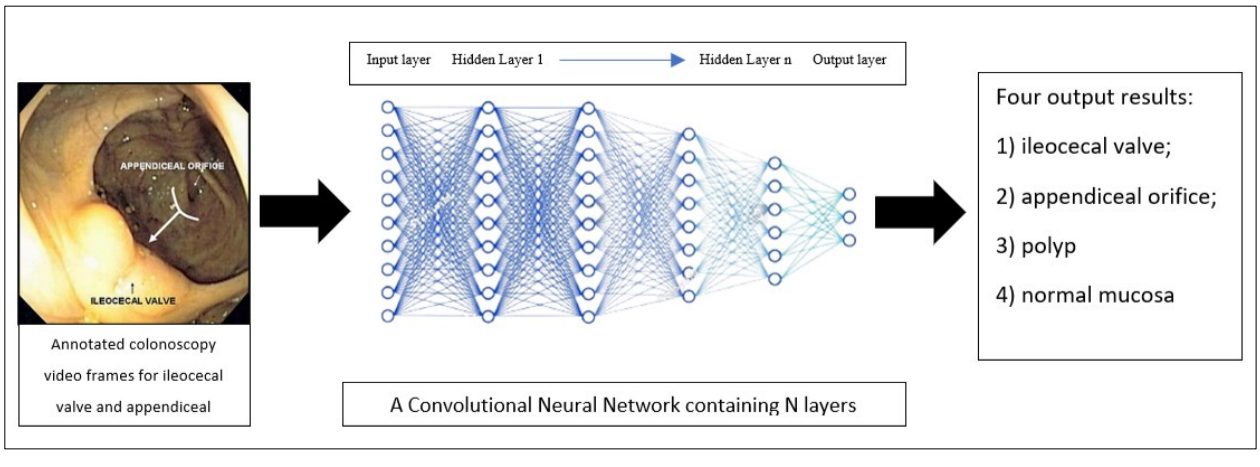


Figure 3 Overview of a Convolutional Neural Network used for training the AI model in Chapter 7. During training on a dataset of input-output pairs, weights of inter-neuron connections are adjusted to optimize classification.

To our knowledge, this is the first model that has been targeted detecting all anatomical landmarks and polyps synchronously. More than 25,000 frames were extracted from 318 colonoscopy videos and divided in three non-overlapping datasets for training, validation, and testing the classification model (**Figure 4**).

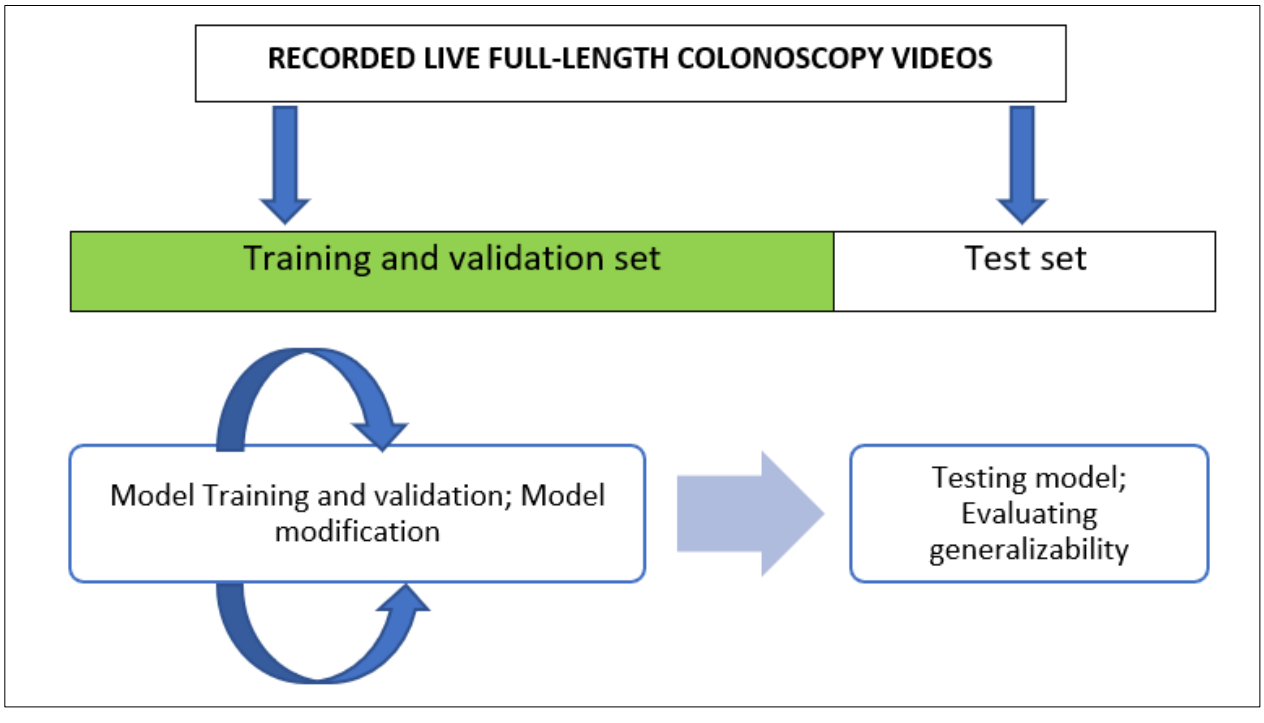


Figure 4 Visualization of training, validation, and test sets

This model could identify both AO and ICV in 18 out of 21 patients (85.71%). The accuracy of the model for differentiating AO from normal mucosa, and ICV from normal mucosa were 86.37% and 86.44%, respectively. Furthermore, the accuracy of the model for differentiating polyps from normal mucosa was 88.57%. The accuracy of the model was >90% when more than two landmarks and/or polyps were present in an image.

The overall quality of practice and individual endoscopists' clinical performance can only be maintained and optimized by continuous clinical evaluation and auditing during and after the speciality training. Thus, the deficiencies and gaps in clinical skills and practice can be recognized and addressed individually for each endoscopist and for institutions to update their endoscopic technologies. Despite recent attempts to design and link auditing tools to the endoscopy practice, their application in routine practice is still challenging primarily due to imposing an excessive administrative and budget burden on hospitals and unstructured endoscopic educational systems. In Canada, a personal digital assistant-based colonoscopy practice audit program, called PAGE-Colonoscopy (PAGE-Colo), was developed as an educational initiative of the Canadian Association of Gastroenterology (CAG) and AstraZeneca Canada Inc.[196] This system includes 52 questions per procedure on patient characteristics, indication for colonoscopy and preparation used. Endoscopists must answer pre-procedural questions about the symptoms, screening of CRC or polyps, and surveillance based on the colonoscopy indications. Post-procedural questions include the adequacy of preparation, the extent of examination, landmarks used to identify the caecum, the time required to complete the procedure, monitoring procedures, medications used, and plans to re-colonoscope the patient. However, it is a lengthy and time-consuming procedure that does not rely on the specific target criteria. In addition, this system has never been tested in real-time practice to determine the optimal time for an audit program. Competingly, our new AI-based model can be used as a novel practice audit and learning tool amenable to a unified screening, intervention, and educational modality, which can be simultaneously implemented during the procedure without spending additional time for data entry. This system targets both procedural, individual, and institutional performance quality. The continuous use of this system would support and improve endoscopists' vigilance and cognitive skill over time by endorsing the most important colonoscopy quality indicators allied by individual professional skills development. It would also significantly contribute to reducing the practice pressure, especially during outbreaks and pandemics due to sparing the cost related to the histopathological examination, definitive surveillance plan provided to the patients on the same day of the colonoscopy, and resolving the need for additional communication between patient, primary and tertiary care providers related to communication and unnecessary visits and laboratory tests. Additionally, this system would obviate the bias raised by self-reported and self-evaluation of practice quality by removing the need for attaining additional skills by the endoscopists due to

the potentials of being easily coupled with the other surveillance models that only need detection of all existing polyps (i.e., location-based resect and discard model).

8.4 Further Perspectives

The future direction of research for optical polyp diagnosis is likely to focus on improving the accuracy and reliability of the diagnosis, as well as developing new techniques for facilitating the recognition of mucosal and vascular patterns. There is a need to improve the current optical classification system to be able to differentiate low- from high-grade dysplasia or SSA from SSP or hyperplastic polyps. Further, current literature lacks evidence on the impact of the use of AI and other machine learning technologies in improving the accuracy of diagnosis, as well as the development of new imaging techniques such as optical coherence tomography (OCT) and confocal microscopy. There is an utmost need for further Investigation to improve the accuracy and consistency of virtual colonoscopy through AI solutions.

Given the fact that the broad application of optical biopsy is required to promote time and cost-effective colonoscopies, it remains necessary to develop automated and accurate measurement systems that are not subject to human perception or preference bias. The effect of such systems must be further evaluated through clinical trials to determine whether they can improve polypectomy practice (i.e., complete removal of polyps with a healthy margin following an appropriate choice of polypectomy technique) and appropriate clinical decision-making about the clinical management of patients with larger polyps (i.e., choosing a correct surveillance interval or treatment option). The current definitions of advanced neoplasia and recommendations of post-colonoscopy surveillance interval heavily rely on endoscopist-based estimates of polyp size. However, with the emergence of more objective and reliable methods for estimating polyp size, it becomes intriguing to contemplate the potential future changes to these definitions and recommendations. The advent of advanced technology could revolutionize our understanding of advanced neoplasia, as well as redefine the associated interval surveillance colonoscopy guidelines. The integration of automated measurement systems with the VSE that can be used with high-definition endoscopes or alongside AI detection and classification platforms would significantly increase colonoscopy efficiency for protecting against PCCRC. Although the performance of VSE seems to be promising, it is only the first generation of

endoscope-integrated polyp size measurement solutions. The next generation of systems will aim to provide automated sizing, which means a number will be displayed the screen indicating definite sizes on instead of superimposed scales requiring skills for adaption to the polyp image.

AI-based colonoscopy is a rapidly evolving discipline of medical research, and as such, several areas hold a significant value for the development of more sophisticated AI algorithms. Research could focus on developing new methods for detecting polyps in difficult-to-reach areas such as sigmoid, proximal colon or colonic flexures. Additionally, the present research is a preliminary attempt to fill a technical gap in the computer-based decision support solutions for automatic detection and differentiation of important colon structures. However, certain measures must be taken into effect to improve this system toward a higher accuracy and sensitivity. Also, it must be tested in a video-based dataset to conclude its effectiveness when the image is constantly moving. Additionally, the combination of this model with other CAD modules is beneficial for developing an automated CRC risk prediction system that can differentiate between low-risk and high-risk screening populations and determine the best surveillance intervals based on the individual needs of each patient. Researchers should aim to continuously and largely collect and annotate endoscopy videos and images from a diverse population of patients including screening and symptomatic population as well as patients with inflammatory bowel disease. This would increase the heterogeneity of data and promote the generalizability of AI platforms in various endoscopic settings.

Another area seeking further attention from researchers and stakeholders is the provision of equal accessibility of the latest CRC prevention technology among all patients disregarding their demographic or socio-economic characteristics. It is imperative to explore means of making AI-based colonoscopy more accessible and affordable for patients, as well as studying its potential to improve patient outcomes and reduce the risk of complications. Another area of interest is to establish financial incentives for using AI systems to avoid the misperception among gastroenterology professionals that these systems are a threat to their practice. This would also aid in establishing clear reporting and auditing processes to ensure that AI-based colonoscopies are in compliance with applicable laws and regulations. This would also be beneficial from patients' perspective since it would enforce a system of cost controls to ensure that AI-based colonoscopies are provided at reasonable costs to patients and health providers.

To optimize clinical workflow, current AI platforms, including the proposed AI model in this thesis, should be deployed through electronic medical records and endoscopy workstations, allowing to use the real-time data for decision support. The new generation of AI platforms should connect to the histopathology registry and automatically provide data from the previous colonoscopies, facilitating the surveillance of individual patients. These combined decision-control platforms should be able to evaluate the quality of each endoscopist's performance and alert him about potential gaps that require setting the appropriate remediation to reach the standards of practice. Furthermore, research attempts are required to design and validate training modules for endoscopists who are beginning to adopt AI technology. As a final point, the gastroenterology societies need to establish certain recommendations or benchmarks for using AI-based technologies so that their application can be standardized among all types of practices. Future research needs to estimate the cost-effectiveness of this system and reproducibility of the outcomes in community-based practices where the ADR is lower due to old colonoscopy devices and suboptimal endoscopist performance.

8.5 Conclusion

This thesis provides evidence on improving the clinical adoption of optical diagnosis, particularly within the resect and discard strategy, the accuracy of polyp size measurement during real-time procedure, and the ability of endoscopists to perform a high-quality and complete colonoscopy. More precisely, this thesis is compromised of seven articles presented in three sections.

Section one comprises three articles suggesting optical and non-optical strategies for facilitating the implementation of resect and discard strategy. It was found that limiting optical diagnosis to polyps 1–3 mm resulted in an excellent safety profile with a very low risk for inappropriate management of advanced adenomas. In addition, it could have reduced about one third of the pathology examinations required, as well as increased the proportion of patients who could have been recommended immediate surveillance, suggesting the feasibility of routine clinical implementation of the resect and discard strategy. Furthermore, two non-optical LBRD and PBRD models were proposed which used the polyp location (LBRD) and polyp number and size (PBRD) as the criteria for assigning surveillance intervals. Both strategies could surpass 90% surveillance interval agreements with pathology-based recommendations and offered a great potential for time- and cost-saving.

Section two consists of two articles. The first article presents a review on the current pitfalls and advancement for accurate polyp size estimation. The body of literature consistency reports a great variability among endoscopist regardless of their speciality for measuring polyp size. Subjective measurement of polyp size may result in underestimation or overestimation. Considering the important clinical consequences of endoscopic size measurement, several studies aimed to evaluate and validate novel tools or structured approaches to reduce interobserver variability and increase the accuracy of endoscopic polyp size measurement. The second article describes a pilot study that evaluated the clinical feasibility of a virtual scale endoscope in real-time colonoscopy. It was found that the VSE offers a higher relative accuracy for polyp measurement compared with visual estimation of polyp size. There is a growing hope that the use of an automated polyp sizing system incorporated into endoscopes will enhance the accuracy of polyp size estimation and enable informed decisions about the appropriate polypectomy, treatment, and follow-up after colonoscopy.

Section three consists of two articles. The first article reviews current state of knowledge on computer-based colonoscopy platforms. The use of AI as an adjunct to standard colonoscopy practices can potentially compete with and outperform endoscopists and improve the accuracy of detection and polyp histology characterization while aiming to deviate from human error, IEE, and unnecessary pathology examination. The current commercially available AI-assisted systems are deficient in supporting endoscopists in monitoring colonoscopy quality, suggesting appropriate polypectomy tools, automatically annotating colonoscopy videos, and generating reports. The second article suggests a DCNN model for detecting cecal structures and differentiating them from polyps and normal colonic mucosa, which could detect and differentiate colon structures with high accuracy. In the future, this model may serve to establish AI platforms that can monitor colonoscopy quality by automatically calculating ADR, CIR, withdrawal time, including photos of the ICV or OA detected during the procedure.

Bibliographic references

1. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2022. 2022
2. Cannizzaro R, Magris R, Maiero S, Fornasarig M, Canzonieri V. Classification of Colon Polyps and Risk of Neoplastic Progression. In: Facciorusso A, Muscatiello N, eds. Colon Polypectomy: Current Techniques and Novel Perspectives. Cham: Springer International Publishing; 2018: 1-11.
3. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**(6 Suppl): S3-43.
4. Pai RK, Bettington M, Srivastava A, Rosty C. An update on the morphology and molecular pathology of serrated colorectal polyps and associated carcinomas. *Mod Pathol* 2019; **32**(10): 1390-415.
5. Tischoff I, Tannapfel A. [Pathohistology of polyps of the gastrointestinal tract]. *Internist (Berl)* 2021; **62**(2): 123-32.
6. 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. *Gastroenterology* 2017; **153**(1): 307-23.
7. Lieberman D, Moravec M, Holub J, Michaels L, Eisen G. Polyp size and advanced histology in patients undergoing colonoscopy screening: implications for CT colonography. *Gastroenterology* 2008; **135**(4): 1100-5.
8. Brenner H, Hoffmeister M, Stegmaier C, Brenner G, Altenhofen L, Haug U. Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies. *Gut* 2007; **56**(11): 1585-9.
9. Rosch T, Altenhofen L, Kretschmann J, et al. Risk of Malignancy in Adenomas Detected During Screening Colonoscopy. *Clin Gastroenterol Hepatol* 2018; **16**(11): 1754-61.
10. Muto T, Bussey HJR, Morson BC. The evolution of cancer of the colon and rectum. *Cancer* 1975; **36**(6): 2251-70.
11. Pickhardt PJ, Pooler BD, Kim DH, Hassan C, Matkowskyj KA, Halberg RB. The Natural History of Colorectal Polyps: Overview of Predictive Static and Dynamic Features. *Gastroenterol Clin North Am* 2018; **47**(3): 515-36.
12. McCashland TM, Brand R, Lyden E, de Garmo P. Gender differences in colorectal polyps and tumors. *Am J Gastroenterol* 2001; **96**(3): 882-6.
13. 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): 90.
14. Ahnen DJ. The American College of Gastroenterology Emily Couric Lecture--the adenoma-carcinoma sequence revisited: has the era of genetic tailoring finally arrived? *Am J Gastroenterol* 2011; **106**(2): 190-8.
15. Koestler DC, Li J, Baron JA, et al. Distinct patterns of DNA methylation in conventional adenomas involving the right and left colon. 2014; **27**(1): 145-55.
16. Yamauchi M, Lochhead P, Morikawa T, et al. Colorectal cancer: a tale of two sides or a continuum? *Gut* 2012; **61**(6): 794-7.
17. Boland CR, Goel A. Microsatellite instability in colorectal cancer. *Gastroenterology* 2010; **138**(6): 2073-87.e3.
18. Markowitz SD, Bertagnolli MMJNEjom. Molecular basis of colorectal cancer. 2009; **361**(25): 2449-60.

19. Martínez ME, Sampliner R, Marshall JR, Bhattacharyya AK, Reid ME, Alberts DSJG. Adenoma characteristics as risk factors for recurrence of advanced adenomas. 2001; **120**(5): 1077-83.
20. Martínez ME, Baron JA, Lieberman DA, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. *Gastroenterology* 2009; **136**(3): 832-41.
21. Pohl H, Robertson DJ, Mott LA, et al. Association between adenoma location and risk of recurrence. *Gastrointest Endosc* 2016; **84**(4): 709-16.
22. Vleugels JLA, Hassan C, Senore C, et al. Diminutive Polyps With Advanced Histologic Features Do Not Increase Risk for Metachronous Advanced Colon Neoplasia. *Gastroenterology* 2019; **156**(3): 623-34 e3.
23. Gupta N, Bansal A, Rao D, et al. Prevalence of advanced histological features in diminutive and small colon polyps. *Gastrointest Endosc* 2012; **75**(5): 1022-30.
24. Rex DK. Making a resect-and-discard strategy work for diminutive colorectal polyps: let's get real. *Endoscopy* 2021; (EFirst).
25. HASSAN C, PICKHARDT PJ, KIM DH, et al. Systematic review: distribution of advanced neoplasia according to polyp size at screening colonoscopy. 2010; **31**(2): 210-7.
26. Taghiakbari M, Pohl H, Djinbachian R, et al. The location-based resect and discard strategy for diminutive colorectal polyps: a prospective clinical study. *Endoscopy* 2021.
27. Schachschal G, Sehner S, Choschzick M, et al. Impact of reassessment of colonic hyperplastic polyps by expert GI pathologists. *Int J Colorectal Dis* 2016; **31**(3): 675-83.
28. Laish I, Sergeev I, Stein A, et al. Risk of metachronous advanced lesions after resection of diminutive and small, non-advanced adenomas. 2019; **43**(2): 201-7.
29. 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**(3): 419-22.
30. Machida H, Sano Y, Hamamoto Y, et al. Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. *Endoscopy* 2004; **36**(12): 1094-8.
31. Apel D, Jakobs R, Schilling D, et al. Accuracy of high-resolution chromoendoscopy in prediction of histologic findings in diminutive lesions of the rectosigmoid. *Gastrointest Endosc* 2006; **63**(6): 824-8.
32. Tischendorf JJ, Wasmuth HE, Koch A, Hecker H, Trautwein C, Winograd R. Value of magnifying chromoendoscopy and narrow band imaging (NBI) in classifying colorectal polyps: a prospective controlled study. *Endoscopy* 2007; **39**(12): 1092-6.
33. De Palma GD, Rega M, Masone S, et al. Conventional colonoscopy and magnified chromoendoscopy for the endoscopic histological prediction of diminutive colorectal polyps: a single operator study. *World J Gastroenterol* 2006; **12**(15): 2402-5.
34. Puig I, Kaltenbach T. Optical Diagnosis for Colorectal Polyps: A Useful Technique Now or in the Future? *Gut Liver* 2018; **12**(4): 385-92.
35. Kudo S-E, Tamura S, Nakajima T, Yamano H-o, Kusaka H, Watanabe HJGe. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. 1996; **44**(1): 8-14.
36. Fu KI, Sano Y, Kato S, et al. Chromoendoscopy using indigo carmine dye spraying with magnifying observation is the most reliable method for differential diagnosis between non-neoplastic and neoplastic colorectal lesions: a prospective study. *Endoscopy* 2004; **36**(12): 1089-93.
37. Konishi K, Kaneko K, Kurahashi T, et al. A comparison of magnifying and nonmagnifying colonoscopy for diagnosis of colorectal polyps: A prospective study. *Gastrointest Endosc* 2003; **57**(1): 48-53.

38. Togashi K, Konishi F. Magnification chromo-colonoscopy. *ANZ J Surg* 2006; **76**(12): 1101-5.
39. Togashi K, Konishi F, Ishizuka T, Sato T, Senba S, Kanazawa K. Efficacy of magnifying endoscopy in the differential diagnosis of neoplastic and non-neoplastic polyps of the large bowel. *Dis Colon Rectum* 1999; **42**(12): 1602-8.
40. Committee AT, Abu Dayyeh BK, Thosani N, 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**(3): 502 e1- e16.
41. Willems P, Djinbachian R, Ditisheim S, et al. Uptake and barriers for implementation of the resect and discard strategy: an international survey. *Endosc Int Open* 2020; **8**(5): E684-E92.
42. Vu HT, Sayuk GS, Hollander TG, et al. Resect and discard approach to colon polyps: real-world applicability among academic and community gastroenterologists. 2015; **60**(2): 502-8.
43. Smith SCL, Siau K, Cannatelli R, et al. Training methods in optical diagnosis and characterization of colorectal polyps: a systematic review and meta-analysis. *Endosc Int Open* 2021; **09**(05): E716-E26.
44. Rex DK. It's not lack of evidence holding back resect and discard. *Gastrointest Endosc* 2022.
45. Taghiakbari M, Mori Y, von Renteln D. Artificial intelligence-assisted colonoscopy: A review of current state of practice and research. *World J Gastroenterol* 2021; **27**(47): 8103-22.
46. Mori YJE. Artificial intelligence and colonoscopy: the time is ripe to begin clinical trials. 2019; **51**(03): 219-20.
47. Mori Y, Neumann H, Misawa M, Kudo S-e, Bretthauer M. Artificial intelligence in colonoscopy - Now on the market. What's next? 2021; **36**(1): 7-11.
48. Hassan C, Sharma P, Mori Y, Bretthauer M, Rex DK. Comparative Performance of Artificial Intelligence Optical Diagnosis Systems for Leaving-In-Situ Colorectal Polyps. *Gastroenterology* 2022.
49. van der Sommen F, de Groof J, Struyvenberg M, et al. Machine learning in GI endoscopy: practical guidance in how to interpret a novel field. *Gut* 2020; **69**(11): 2035-45.
50. Song EM, Park B, Ha CA, et al. Endoscopic diagnosis and treatment planning for colorectal polyps using a deep-learning model. *Sci Rep* 2020; **10**(1): 30.
51. Wang P, Berzin TM, Glissen Brown JR, et al. Real-time automatic detection system increases colonoscopic polyp and adenoma detection rates: a prospective randomised controlled study. *Gut* 2019; **68**(10): 1813-9.
52. Poon CCY, Jiang Y, Zhang R, et al. AI-doscopist: a real-time deep-learning-based algorithm for localising polyps in colonoscopy videos with edge computing devices. *NPJ Digit Med* 2020; **3**(1): 73.
53. Zhang R, Zheng Y, Mak TW, et al. Automatic Detection and Classification of Colorectal Polyps by Transferring Low-Level CNN Features From Nonmedical Domain. *IEEE J Biomed Health Inform* 2017; **21**(1): 41-7.
54. Hoerter N, Gross SA, Liang PS. Artificial Intelligence and Polyp Detection. *Curr Treat Options Gastroenterol* 2020; **18**(1): 120-36.
55. Hassan C, Spadaccini M, Iannone A, et al. Performance of artificial intelligence in colonoscopy for adenoma and polyp detection: a systematic review and meta-analysis. *Gastrointest Endosc* 2021; **93**(1): 77-85 e6.
56. El Hajjar A, Rey JF. Artificial intelligence in gastrointestinal endoscopy: general overview. *Chin Med J (Engl)* 2020; **133**(3): 326-34.

57. Lui TKL, Guo CG, Leung WK. Accuracy of artificial intelligence on histology prediction and detection of colorectal polyps: a systematic review and meta-analysis. *Gastrointest Endosc* 2020; **92**(1): 11-22.e6.
58. Rex DK, Berzin TM, Mori Y. Artificial Intelligence Improves Detection at Colonoscopy: Why Aren't We All Already Using It? *Gastroenterology* 2022; **163**(1): 35-7.
59. Lui TK, Guo C-G, Leung WKJGe. Accuracy of artificial intelligence on histology prediction and detection of colorectal polyps: a systematic review and meta-analysis. 2020; **92**(1): 11-22. e6.
60. Gupta S, Balasubramanian BA, Fu T, Genta RM, Rockey DC, Lash R. Polyps with advanced neoplasia are smaller in the right than in the left colon: implications for colorectal cancer screening. *Clin Gastroenterol Hepatol* 2012; **10**(12): 1395-401 e2.
61. He X, Hang D, Wu K, et al. Long-term Risk of Colorectal Cancer After Removal of Conventional Adenomas and Serrated Polyps. *Gastroenterology* 2020; **158**(4): 852-61 e4.
62. Gupta S, Lieberman D, Anderson JC, et al. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2020; **158**(4): 1131-53 e5.
63. Kaltenbach T, Anderson JC, Burke CA, et al. Endoscopic Removal of Colorectal Lesions: Recommendations by the US Multi-Society Task Force on Colorectal Cancer. *Official journal of the American College of Gastroenterology | ACG* 2020; **115**(3).
64. Pimentel-Nunes P, Libânio D, Bastiaansen BAJ, et al. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2022. *Endoscopy* 2022; **54**(06): 591-622.
65. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. 2017; **49**(03): 270-97.
66. Chang CY, Chiu HM, Wang HP, et al. An endoscopic training model to improve accuracy of colonic polyp size measurement. *Int J Colorectal Dis* 2010; **25**(5): 655-60.
67. Gopalswamy N, Shenoy VN, Choudhry U, et al. Is in vivo measurement of size of polyps during colonoscopy accurate? *Gastrointest Endosc* 1997; **46**(6): 497-502.
68. Han S-K, Kim H, Kim J-w, Kim H-S, Kim S-Y, Park H-J. Usefulness of a Colonoscopy Cap with an External Grid for the Measurement of Small-Sized Colorectal Polyps: A Prospective Randomized Trial. 2021; **10**(11): 2365.
69. Hyun YS, Han DS, Bae JH, Park HS, Eun CS. Graduated injection needles and snares for polypectomy are useful for measuring colorectal polyp size. *Digestive and Liver Disease* 2011; **43**(5): 391-4.
70. Masato Y, Yuichi S, Daisuke U, et al. Virtual scale function of gastrointestinal endoscopy for accurate polyp size estimation in real-time: a preliminary study. *Journal of Biomedical Optics* 2021; **26**(9): 1-10.
71. Jen J, Powell SM, Papadopoulos N, et al. Molecular determinants of dysplasia in colorectal lesions. *Cancer Res* 1994; **54**(21): 5523-6.
72. Kalyta A, De Vera MA, Peacock S, et al. Canadian Colorectal Cancer Screening Guidelines: Do They Need an Update Given Changing Incidence and Global Practice Patterns? *Curr Oncol* 2021; **28**(3): 1558-70.
73. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; **366**(8): 687-96.
74. Rutter MD, Beintaris I, Valori R, et al. World Endoscopy Organization consensus statements on post-colonoscopy and post-imaging colorectal cancer. 2018; **155**(3): 909-25. e3.

75. Arain MA, Sawhney M, Sheikh S, et al. CIMP status of interval colon cancers: another piece to the puzzle. 2010; **105**(5): 1189-95.
76. Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. *Am J Gastroenterol* 2012; **107**(9): 1315-29; quiz 4, 30.
77. Vinsard DG, Mori Y, Misawa M, et al. Quality assurance of computer-aided detection and diagnosis in colonoscopy. *Gastrointest Endosc* 2019; **90**(1): 55-63.
78. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc* 2015; **81**(1): 31-53.
79. Johnson DA, Barkun AN, Cohen LB, et al. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the US Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol* 2014; **109**(10): 1528-45.
80. Singh H, Nugent Z, Demers AA, Kliewer EV, Mahmud SM, Bernstein CNJG. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. 2010; **139**(4): 1128-37.
81. Baxter NN, Sutradhar R, Forbes SS, Paszat LF, Saskin R, Rabeneck LJG. Analysis of administrative data finds endoscopist quality measures associated with postcolonoscopy colorectal cancer. 2011; **140**(1): 65-72.
82. Rabeneck L, Paszat LF, Saskin RJCG, Hepatology. Endoscopist specialty is associated with incident colorectal cancer after a negative colonoscopy. 2010; **8**(3): 275-9.
83. Hassan C, Rex DK, Zullo A, Kaminski MFJUEgj. Efficacy and cost-effectiveness of screening colonoscopy according to the adenoma detection rate. 2015; **3**(2): 200-7.
84. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014; **370**(14): 1298-306.
85. Su JR, Li Z, Shao XJ, et al. Impact of a real-time automatic quality control system on colorectal polyp and adenoma detection: a prospective randomized controlled study (with videos). *Gastrointest Endosc* 2020; **91**(2): 415-24.e4.
86. Repici A, Badalamenti M, Maselli R, et al. Efficacy of Real-Time Computer-Aided Detection of Colorectal Neoplasia in a Randomized Trial. *Gastroenterology* 2020; **159**(2): 512-20.e7.
87. Wang P, Liu X, Berzin TM, et al. Effect of a deep-learning computer-aided detection system on adenoma detection during colonoscopy (CADe-DB trial): a double-blind randomised study. *The Lancet Gastroenterology & Hepatology* 2020; **5**(4): 343-51.
88. Glissen Brown JR, Mansour NM, Wang P, et al. Deep Learning Computer-aided Polyp Detection Reduces Adenoma Miss Rate: A United States Multi-center Randomized Tandem Colonoscopy Study (CADeT-CS Trial). *Clinical Gastroenterology and Hepatology* 2022; **20**(7): 1499-507.e4.
89. Wallace MB, Sharma P, Bhandari P, et al. Impact of artificial intelligence on miss rate of colorectal neoplasia. 2022.
90. Misawa M, Kudo SE, Mori Y, et al. Artificial Intelligence-Assisted Polyp Detection for Colonoscopy: Initial Experience. *Gastroenterology* 2018; **154**(8): 2027-9 e3.
91. Byrne MF, Shahidi N, Rex DK. Will Computer-Aided Detection and Diagnosis Revolutionize Colonoscopy? *Gastroenterology* 2017; **153**(6): 1460-4 e1.
92. 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**(1): 94-100.
93. Shahidi N, Rex DK, Kaltenbach T, Rastogi A, Ghalehjegh SH, Byrne MFJG. Use of Endoscopic Impression, Artificial Intelligence, and Pathologist Interpretation to Resolve Discrepancies Between Endoscopy and Pathology Analyses of Diminutive Colorectal Polyps. *Gastroenterology* 2020; **158**(3): 783-5. e1.

94. Urban G, Tripathi P, Alkayali T, et al. Deep Learning Localizes and Identifies Polyps in Real Time With 96% Accuracy in Screening Colonoscopy. *Gastroenterology* 2018; **155**(4): 1069-78 e8.
95. Wang Y, Tavanapong W, Wong JS, Oh J, de Groen PC. Detection of quality visualization of appendiceal orifices using local edge cross-section profile features and near pause detection. *IEEE Trans Biomed Eng* 2010; **57**(3): 685-95.
96. 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**(8): 683-91.
97. Vleugels JLA, Hazewinkel Y, Dijkgraaf MGW, et al. Optical diagnosis expanded to small polyps: post-hoc analysis of diagnostic performance in a prospective multicenter study. *Endoscopy* 2019; **51**(3): 244-52.
98. Singh H, Bay D, Ip S, et al. Pathological reassessment of hyperplastic colon polyps in a city-wide pathology practice: implications for polyp surveillance recommendations. *Gastrointest Endosc* 2012; **76**(5): 1003-8.
99. Anderson JC, Lisovsky M, Greene MA, Hagen C, Srivastava A. Factors Associated With Classification of Hyperplastic Polyps as Sessile Serrated Adenomas/Polyps on Morphologic Review. *J Clin Gastroenterol* 2018; **52**(6): 524-9.
100. Baldin RKS, Anselmi Júnior RA, Azevedo M, et al. Interobserver variability in histological diagnosis of serrated colorectal polyps. *Journal of Coloproctology (Rio de Janeiro)* 2015; **35**: 193-7.
101. Mori Y, Kudo S-e, Misawa M, et al. Real-time use of artificial intelligence in identification of diminutive polyps during colonoscopy: a prospective study. 2018; **169**(6): 357-66.
102. Weigt J, Repici A, Antonelli G, et al. Performance of a new integrated computer-assisted system (CADe/CADx) for detection and characterization of colorectal neoplasia. *Endoscopy* 2022; **54**(2): 180-4.
103. Pohl H, Robertson DJJCG, Hepatology. Colorectal cancers detected after colonoscopy frequently result from missed lesions. 2010; **8**(10): 858-64.
104. Ponugoti PL, Cummings OW, Rex DK. Risk of cancer in small and diminutive colorectal polyps. *Dig Liver Dis* 2017; **49**(1): 34-7.
105. Taghiakbari M, Pohl H, Djinbachian R, et al. What size cutoff level should be used to implement optical polyp diagnosis? *Endoscopy* 2022.
106. Hassan C, Antonelli G, Dumonceau J-M, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2020. *Endoscopy* 2020; **52**(08): 687-700.
107. Bonithon-Kopp C, Piard F, Fenger C, et al. Colorectal adenoma characteristics as predictors of recurrence. *Dis Colon Rectum* 2004; **47**(3): 323-33.
108. Saini SD, Kim HM, Schoenfeld P. Incidence of advanced adenomas at surveillance colonoscopy in patients with a personal history of colon adenomas: a meta-analysis and systematic review. *Gastrointest Endosc* 2006; **64**(4): 614-26.
109. 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**(12): 1704-13.
110. Ahmad A, Moorghen M, Wilson A, et al. Implementation of optical diagnosis with a "resect and discard" strategy in clinical practice: DISCARD3 study. 2022.
111. McGill SK, Soetikno R, Rastogi A, et al. Endoscopists can sustain high performance for the optical diagnosis of colorectal polyps following standardized and continued training. 2015; **10**(03): 200-6.

112. Vleugels JL, Dijkgraaf MG, Hazewinkel Y, et al. 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. 2018; **154**(6): 1682-93. e1.
113. Excellence NIfHaC. Virtual chromoendoscopy to assess colorectal polyps during colonoscopy. Major recommendation setting quality thresholds for optical diagnosis in the UK. 2017.
114. Bisschops R, East JE, Hassan C, et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2019. *Endoscopy* 2019; **51**(12): 1155-79.
115. Rex DK. Narrow-band imaging without optical magnification for histologic analysis of colorectal polyps. *Gastroenterology* 2009; **136**(4): 1174-81.
116. 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**(3): 599-607 e1.
117. Gupta N, Kaltenbach T, Sato T, Bansal A, Soetikno RM, Rastogi AJGE. Tu1475 Diagnosis Time Determines the Accuracy of Optical Diagnosis of Diminutive Polyp Histology. 2013; **77**(5): AB553-AB4.
118. Patel SG, Schoenfeld P, Kim HM, et al. Real-Time Characterization of Diminutive Colorectal Polyp Histology Using Narrow-Band Imaging: Implications for the Resect and Discard Strategy. *Gastroenterology* 2016; **150**(2): 406-18.
119. Rastogi A, Rao DS, Gupta N, et al. 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**(3): 390-8.
120. American Society of Gastrointestinal Endoscopy (ASGE) Optical diagnosis of colorectal polyps (OLV004) [Internet] Downers Grove: ASGE. 2013.
121. 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**(3): 572-6.
122. Ignjatovic A, Thomas-Gibson S, East JE, et al. 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**(1): 128-33.
123. 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**(5): 887-95.
124. JE IJ, 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**(6): 963-70.
125. Iacucci M, Trovato C, Daperno M, et al. Development and validation of the SIMPLE endoscopic classification of diminutive and small colorectal polyps. *Endoscopy* 2018; **50**(8): 779-89.
126. Kanao H, Tanaka S, Oka S, Hirata M, Yoshida S, Chayama KJGe. Narrow-band imaging magnification predicts the histology and invasion depth of colorectal tumors. 2009; **69**(3): 631-6.
127. Oka S, Tanaka S, Takata S, Kanao H, Chayama KJDE. Clinical usefulness of narrow band imaging magnifying classification for colorectal tumors based on both surface pattern and microvessel features. 2011; **23**: 101-5.
128. Oba S, Tanaka S, Oka S, et al. Characterization of colorectal tumors using narrow-band imaging magnification: combined diagnosis with both pit pattern and microvessel features. 2010; **45**(9): 1084-92.

129. Sumimoto K, Tanaka S, Shigita K, et al. Clinical impact and characteristics of the narrow-band imaging magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. *Gastrointest Endosc* 2017; **85**(4): 816-21.
130. Komeda Y, Kashida H, Sakurai T, et al. Magnifying narrow band imaging (NBI) for the diagnosis of localized colorectal lesions using the Japan NBI Expert Team (JNET) classification. 2017; **93**(Suppl. 1): 49-54.
131. Sano Y, Ikematsu H, Fu KI, et al. Meshed capillary vessels by use of narrow-band imaging for differential diagnosis of small colorectal polyps. *Gastrointest Endosc* 2009; **69**(2): 278-83.
132. Katagiri A, Fu KI, Sano Y, et al. Narrow band imaging with magnifying colonoscopy as diagnostic tool for predicting histology of early colorectal neoplasia. *Aliment Pharmacol Ther* 2008; **27**(12): 1269-74.
133. Henry ZH, Yeaton P, Shami VM, et al. Meshed capillary vessels found on narrow-band imaging without optical magnification effectively identifies colorectal neoplasia: a North American validation of the Japanese experience. 2010; **72**(1): 118-26.
134. Bisschops R, Hassan C, Bhandari P, et al. BASIC (BLI Adenoma Serrated International Classification) classification for colorectal polyp characterization with blue light imaging. *Endoscopy* 2018; **50**(3): 211-20.
135. Sano Y, Tanaka S, Kudo SE, et al. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. *Dig Endosc* 2016; **28**(5): 526-33.
136. Uraoka T, Saito Y, Ikematsu H, Yamamoto K, Sano YJDE. Sano's capillary pattern classification for narrow-band imaging of early colorectal lesions. 2011; **23**: 112-5.
137. Lee A, Tutticci N. Enhancing polyp detection: technological advances in colonoscopy imaging. *Transl Gastroenterol Hepatol* 2021; **6**: 61.
138. Tada M, Katoh S, Kohli Y, Kawai KJE. On the dye spraying method in colonofiberscopy. 1976; **8**(02): 70-4.
139. Kahi CJ, Li X, Eckert GJ, Rex DKJGe. High colonoscopic prevalence of proximal colon serrated polyps in average-risk men and women. 2012; **75**(3): 515-20.
140. Kaminski MF, Hassan C, Bisschops R, et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2014; **46**(5): 435-49.
141. Kahi CJ, Anderson JC, Waxman I, et al. High-definition chromocolonoscopy vs. high-definition white light colonoscopy for average-risk colorectal cancer screening. 2010; **105**(6): 1301-7.
142. Hurt C, Ramaraj R, Farr A, et al. Feasibility and economic assessment of chromocolonoscopy for detection of proximal serrated neoplasia within a population-based colorectal cancer screening programme (CONSCOP): an open-label, randomised controlled non-inferiority trial. *Lancet Gastroenterol Hepatol* 2019; **4**(5): 364-75.
143. Subramanian V, Mannath J, Hawkey C, Ragunath KJE. High definition colonoscopy vs. standard video endoscopy for the detection of colonic polyps: a meta-analysis. 2011; **43**(06): 499-505.
144. Di Caro S, Fini L, Vega R, et al. Multicentre randomised controlled trial comparing standard and high resolution optical technologies in colorectal cancer screening. 2019; **10**(3): 244-52.
145. East JE, Vleugels JL, Roelandt P, et al. Advanced endoscopic imaging: European Society of Gastrointestinal Endoscopy (ESGE) Technology Review. *Endoscopy* 2016; **48**(11): 1029-45.
146. Djinbachian R, Dube AJ, von Renteln D. Optical Diagnosis of Colorectal Polyps: Recent Developments. *Curr Treat Options Gastroenterol* 2019; **17**(1): 99-114.

147. Atkinson NSS, Ket S, Bassett P, 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; **157**(2): 462-71.
148. Aziz M, Desai M, Hassan S, et al. Improving serrated adenoma detection rate in the colon by electronic chromoendoscopy and distal attachment: systematic review and meta-analysis. 2019; **90**(5): 721-31. e1.
149. Klare P, Haller B, Wormbt S, et al. Narrow-band imaging vs. high definition white light for optical diagnosis of small colorectal polyps: a randomized multicenter trial. *Endoscopy* 2016; **48**(10): 909-15.
150. Ashktorab H, Etaati F, Rezaeean F, et al. Can optical diagnosis of small colon polyps be accurate? Comparing standard scope without narrow banding to high definition scope with narrow banding. *World J Gastroenterol* 2016; **22**(28): 6539-46.
151. Bhandari P, Thayalasekaran S, Keisslich R, et al. Detection and characterization of colorectal polyps using high-definition white light and i-Scan: Evidence-based consensus recommendations using a modified Delphi process. *United European Gastroenterol J* 2018; **6**(5): 748-54.
152. Testoni PA, Notaristefano C, Vailati C, Di Leo M, Viale E. High-definition colonoscopy with i-Scan: better diagnosis for small polyps and flat adenomas. *World J Gastroenterol* 2012; **18**(37): 5231-9.
153. Kidambi TD, Terdiman JP, El-Nachef N, Singh A, Kattah MG, Lee JK. Effect of I-scan Electronic Chromoendoscopy on Detection of Adenomas During Colonoscopy. *Clin Gastroenterol Hepatol* 2019; **17**(4): 701-8.e1.
154. Bisschops R, Tejpar S, Willekens H, De Hertogh G, Van Cutsem E. Virtual chromoendoscopy (I-SCAN) detects more polyps in patients with Lynch syndrome: a randomized controlled crossover trial. *Endoscopy* 2017; **49**(4): 342-50.
155. Klenske E, Zopf S, Neufert C, et al. I-scan optical enhancement for the in vivo prediction of diminutive colorectal polyp histology: results from a prospective three-phased multicentre trial. 2018; **13**(5): e0197520.
156. Kaltenbach T, Rastogi A, Rouse RV, et al. Real-time optical diagnosis for diminutive colorectal polyps using narrow-band imaging: the VALID randomised clinical trial. 2015; **64**(10): 1569-77.
157. Shung DL, Byrne MF. How Artificial Intelligence Will Impact Colonoscopy and Colorectal Screening. *Gastrointest Endosc Clin N Am* 2020; **30**(3): 585-95.
158. Misawa M, Kudo S-e, Mori Y, et al. Characterization of colorectal lesions using a computer-aided diagnostic system for narrow-band imaging endocytoscopy. 2016; **150**(7): 1531-2. e3.
159. Hassan C, Balsamo G, Lorenzetti R, Zullo A, Antonelli G. Artificial Intelligence Allows Leaving-In-Situ Colorectal Polyps. *Clinical Gastroenterology and Hepatology* 2022; **20**(11): 2505-13.e4.
160. Taghiakbari M, Hammar C, Frenn M, et al. Non-optical polyp-based resect and discard strategy: A prospective clinical study. *World J Gastroenterol* 2022; **28**(19): 2137-47.
161. Atalaia-Martins C, Marcos P, Leal C, et al. Variation between Pathological Measurement and Endoscopically Estimated Size of Colonic Polyps. *GE Port J Gastroenterol* 2019; **26**(3): 163-8.
162. Chaptini L, Chaaya A, Depalma F, Hunter K, Peikin S, Laine LJGe. Variation in polyp size estimation among endoscopists and impact on surveillance intervals. 2014; **80**(4): 652-9.
163. Vleugels JLA, Dekker E. Does polyp size matter? *Endosc Int Open* 2017; **5**(8): E746-E8.
164. von Renteln D, Djinbachian R, Zarandi-Nowroozi M, Taghiakbari M. Measuring size of smaller colorectal polyps using a virtual scale function during endoscopies. *Gut* 2022: gutjnl-2022-328654.

165. Telford JJ, Levy AR, Sambrook JC, Zou D, Enns RA. The cost-effectiveness of screening for colorectal cancer. *Canadian Medical Association Journal* 2010; **182**(12): 1307.
166. Anderson JC, Butterly LF. Colonoscopy: quality indicators. *Clin Transl Gastroenterol* 2015; **6**(2): e77.
167. Taghiakbari M, Mori Y, von Renteln D. Artificial intelligence-assisted colonoscopy: A review of current state of practice and research. *World J Gastroenterol* 2021; **27**(47): 8103-22.
168. Jung Y, Lee S-H. How Do I Overcome Difficulties in Insertion? *Clin Endosc* 2012; **45**(3): 278-81.
169. Le Berre C, Sandborn WJ, Aridhi S, et al. Application of Artificial Intelligence to Gastroenterology and Hepatology. *Gastroenterology* 2020; **158**(1): 76-94 e2.
170. Mori Y, Kaminski MF, Hassan C, Bretthauer M. Clinical trial designs for artificial intelligence in gastrointestinal endoscopy. *The Lancet Gastroenterology & Hepatology* 2022; **7**(9): 785-6.
171. Ahmad OF, Soares AS, Mazomenos E, et al. Artificial intelligence and computer-aided diagnosis in colonoscopy: current evidence and future directions. *Lancet Gastroenterol Hepatol* 2019; **4**(1): 71-80.
172. Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. *Ann Intern Med* 2011; **154**(1): 22-30.
173. 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.
174. Rex DKJGe. Still photography versus videotaping for documentation of cecal intubation: a prospective study. 2000; **51**(4): 451-9.
175. Mark-Christensen A, Brandsborg S, Iversen LH. Magnetic endoscopic imaging as an adjuvant to elective colonoscopy: a systematic review and meta-analysis of randomized controlled trials. *Endoscopy* 2015; **47**(3): 251-61.
176. Shah SG, Brooker JC, Williams CB, Thapar C, Suzuki N, Saunders BP. The variable stiffness colonoscope: Assessment of efficacy by magnetic endoscope imaging. *Gastrointestinal Endoscopy* 2002; **56**(2): 195-201.
177. Garborg K, Wiig H, Hasund A, et al. Gradual stiffness versus magnetic imaging-guided variable stiffness colonoscopes: A randomized noninferiority trial. *United European Gastroenterol J* 2017; **5**(1): 128-33.
178. Williams CB. Insertion technique. Colonoscopy: principles and practice: Blackwell Publishing Ltd, Chichester, UK; 2009: 537-59.
179. Johnson DA, Gurney MS, Volpe RJ, et al. A prospective study of the prevalence of colonic neoplasms in asymptomatic patients with an age-related risk. 1990; **85**(8).
180. Foutch PG, Mai H, Pardy K, et al. Flexible sigmoidoscopy may be ineffective for secondary prevention of colorectal cancer in asymptomatic, average-risk men. 1991; **36**(7): 924-8.
181. Kadakia SC, Wrobleski CS, Kadakia AS, Meier NJJGe. Prevalence of proximal colonic polyps in average-risk asymptomatic patients with negative fecal occult blood tests and flexible sigmoidoscopy. 1996; **44**(2): 112-7.
182. Lieberman DA, Weiss DG, Bond JH, et al. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. 2000; **343**(3): 162-8.
183. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *N Engl J Med* 2000; **343**(3): 169-74.

184. Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross MEJNEjom. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. 2004; **351**(26): 2704-14.
185. Schoenfeld P, Cash B, Flood A, et al. Colonoscopic screening of average-risk women for colorectal neoplasia. 2005; **352**(20): 2061-8.
186. Rathgaber SW, Wick TMJGe. Colonoscopy completion and complication rates in a community gastroenterology practice. 2006; **64**(4): 556-62.
187. Niv Y, Hazazi R, Levi Z, Fraser GJDd, sciences. Screening colonoscopy for colorectal cancer in asymptomatic people: a meta-analysis. 2008; **53**(12): 3049-54.
188. Kim DH, Lee SY, Choi KS, et al. The usefulness of colonoscopy as a screening test for detecting colorectal polyps. 2007; **54**(80): 2240-2.
189. Stanek SR, Tavanapong W, Wong J, et al. SAPPHIRE: a toolkit for building efficient stream programs for medical video analysis. *Comput Methods Programs Biomed* 2013; **112**(3): 407-21.
190. Filip D, Gao X, Angulo-Rodriguez L, et al. Colometer: a real-time quality feedback system for screening colonoscopy. *World J Gastroenterol* 2012; **18**(32): 4270-7.
191. Gong D, Wu L, Zhang J, et al. Detection of colorectal adenomas with a real-time computer-aided system (ENDOANGEL): a randomised controlled study. *The Lancet Gastroenterology & Hepatology* 2020; **5**(4): 352-61.
192. Cao Y, Liu D, Tavanapong W, Wong J, Oh J, Groen PCd. Automatic Classification of Images with Appendiceal Orifice in Colonoscopy Videos. 2006 International Conference of the IEEE Engineering in Medicine and Biology Society; 2006 30 Aug.-3 Sept. 2006; 2006. p. 2349-52.
193. Low DJ, Hong Z, Khan R, Bansal R, Gimpaya N, Grover SC. Automated detection of cecal intubation with variable bowel preparation using a deep convolutional neural network. *Endosc Int Open* 2021; **9**(11): E1778-E84.
194. Karnes WE, Ninh A, Dao T, Requa J, Samarasena JB. Sa1925 REAL-TIME IDENTIFICATION OF ANATOMIC LANDMARKS DURING COLONOSCOPY USING DEEP LEARNING. *Gastrointestinal Endoscopy* 2018; **87**(6): AB252.
195. Li Y, Ding A, Cao Y, Liu B, Chen S, Liu X. Detection of Endoscope Withdrawal Time in Colonoscopy Videos. 2021 20th IEEE International Conference on Machine Learning and Applications (ICMLA); 2021 13-16 Dec. 2021; 2021. p. 67-74.
196. Armstrong D, Hollingworth R, Gardiner T, et al. Practice Audit in Gastroenterology (PAGE) program: a novel approach to continuing professional development. *Can J Gastroenterol* 2006; **20**(6): 405-10.

Appendix 1

Chapter 4 and 5-Video 1 Examples of VSE polyp size measurements during colonoscopies.

Please find this video in **Supplementary File**.