

Vision, Gaze and Advances in Endoluminal Control Systems

ARUN GANAN SIVANANTHAN

BSC MBBS MRCP

INSTITUTE OF GLOBAL HEALTH INNOVATION

IMPERIAL COLLEGE LONDON

2025

This thesis is submitted to Imperial College London in partial fulfilment of the requirements for the degree of Doctor of Philosophy (PhD). Except for where indicated, it presents entirely my own work and describes the results of my own research.

Copyright Declaration

The copyright of this thesis rests with the author. Unless otherwise indicated, its contents are licensed under a Creative Commons Attribution-Non Commercial 4.0 International Licence (CC BY-NC).

Under this licence, you may copy and redistribute the material in any medium or format. You may also create and distribute modified versions of the work. This is on the condition that: you credit the author and do not use it, or any derivative works, for a commercial purpose.

When reusing or sharing this work, ensure you make the licence terms clear to others by naming the licence and linking to the licence text. Where a work has been adapted, you should indicate that the work has been changed and describe those changes.

Please seek permission from the copyright holder for uses of this work that are not included in this licence or permitted under UK Copyright Law.

Abstract

The field of luminal endoscopy has recently evolved rapidly, expanding both its diagnostic and therapeutic capabilities. As gastrointestinal cancer continues to rise in prevalence, endoscopy must advance to improve prevention, early detection, and minimally invasive treatment. Significant effort has focused on enhancing imaging technologies and therapeutic adjuncts, enabling earlier diagnosis and more effective management of luminal pathology. Despite these advances, the fundamental endoscope control system has remained largely unchanged for nearly half a century, relying on a bimanually operated flexible instrument controlled by dual wheels and cables.

The role of vision and gaze in endoscopy remains poorly defined yet represents an emerging area of research. Gaze analysis technology offers insight into visual search patterns during lesion detection. A systematic review demonstrates its potential as an objective tool to evaluate detection performance and assess optical technologies designed to enhance visualisation. A meta-analysis of real-time artificial intelligence–assisted systems confirms improved detection of precursor lesions. A cross-sectional survey of endoscopists further highlights persistent challenges in orientation and spatial control during procedures.

Review of current control systems and adjunctive tools reveals ongoing attempts to optimise endoscopic manipulation. However, the intrinsic flexibility of the endoscope presents mechanical challenges in delivering advanced therapy, contributing to a steep learning curve that confines complex procedures to a small cohort of skilled operators. Recent work has explored robotic integration to enhance intuitive control. A systematic review of predominantly experimental robotic platforms identifies multiple systems at varying stages of development, though most remain costly and confined to trial settings.

This thesis introduces gaze control as a novel paradigm in endoscopic manipulation. Integration of eye-tracking technology with a robotised conventional endoscope enabled development of the first hands-free gaze-controlled system, demonstrating feasibility in benchtop and human trials. The refined iGAZE2 system represents proof of concept for a new approach to endoscopic control.

Acknowledgements

This thesis is dedicated to my parents, without whose sacrifice I could never have achieved this. My father would have been immensely proud to see this thesis, and my mother has been a constant source of encouragement, advice, and guidance throughout. I am also grateful to my sister, whose early enthusiasm for science helped inspire my own interest in the field.

I would like to express my deepest gratitude to my supervisors. I was fortunate to benefit from Nisha's expertise, guidance, and direction in such a novel area of research, as well as supporting me with excellent advanced endoscopy training. It was an immense privilege to be supervised by Ara Darzi, whose insightful reviews and input enriched every stage of my research journey. I am also thankful to Kinesh Patel and Laksh Ayaru for their availability, feedback, and support throughout my projects.

My time at the Hamlyn Robotics Centre was an extraordinary experience, surrounded by brilliant minds pushing the boundaries of medical robotics. I am particularly grateful to George Mylonas, Adrian Rubio-Solis, Alexandros Kogkas, and Kaizhe Jin. Collaborating with such a bright, talented, and international group was an honour.

I greatly valued the advice and camaraderie of fellow researchers Javed Ahmed, Ben Glover, Scarlet Nazarian, Charlie Hateley, Ben Mullish, James Alexander, Luke Tyson, Rob Perry, Charlie Skinner, and Ravi Aggarwal. I am also grateful for Sam Shribman, Paul Arkell, Abdullah Bashir, Josh Shur, Jon King, Sophie Carpenter and Victoria Nicholas, who provided perspective, and much-needed balance beyond research.

Special thanks to Shiva Radhakrishnan, whose recent experience and surprisingly sage advice were invaluable in navigating the challenges of PhD research. Finally, I offer my sincere thanks to Georgie Kerry for her unwavering support, patience, and belief in me.

Table of Contents

1. INTRODUCTION	11
1.1 PROLOGUE	11
1.2 AIMS OF THIS RESEARCH	11
1.3 HYPOTHESIS	12
1.4 THESIS OVERVIEW.....	13
1.5 THE ORIGINAL CONTRIBUTIONS OF THIS THESIS	15
1.6 PUBLICATIONS ARISING FROM THESIS	15
1.7 POSTERS ARISING FROM THESIS.....	16
2. ENDOSCOPIC LESION DETECTION: A REVIEW OF GAZE ANALYSIS IN ENDOSCOPY	17
2.1 BACKGROUND:.....	17
2.2 THE ROLE OF ENDOSCOPY IN LESION DETECTION.....	19
2.3 IMAGING IN ENDOSCOPY	22
2.4 GAZE ANALYSIS IN ENDOSCOPY	25
2.5 CONCLUSION	38
3. AI IN ENDOSCOPY: A META-ANALYSIS OF COMPUTER AIDED DIAGNOSTIC ENDOSCOPY (CADE) IN LESION DETECTION	40
3.1 BACKGROUND.....	40
3.2 METHODOLOGY:.....	42
3.3 RESULTS	46
3.4 DISCUSSION	55
3.5 CONCLUSION	57
4. ORIENTATION IN ENDOSCOPY: A CROSS SECTIONAL DESCRIPTIVE SURVEY OF ENDOSCOPISTS ORIENTATION DURING ENDOSCOPY	58
4.1 BACKGROUND:.....	58
4.2 METHODOLOGY	63
4.3 RESULTS	67
4.4 DISCUSSION	69
4.5 CONCLUSION	71
5. THERAPEUTIC ENDOSCOPY: THE INTERVENTIONAL ENDOSCOPIST' TOOLBOX	72
5.1 BACKGROUND.....	72
5.2 THERAPEUTIC LUMINAL ENDOSCOPY	73
5.3 REVIEW OF ESD TOOLS AVAILABLE.....	78
5.4 CONCLUSION	90
6. ENDOSCOPE CONTROL SYSTEMS AND THE RISE OF ROBOTIC ENDOSCOPY	91
6.1 BACKGROUND.....	91
6.2 THE CURRENT ENDOSCOPE AND CONTROL SYSTEM.....	92
6.3 CHALLENGES OF THE CURRENT ENDOSCOPE CONTROL SYSTEM	97
6.4 A REVIEW OF CURRENT ROBOTIC ENDOSCOPE PLATFORMS.....	99
6.5 CONCLUSION	113
7. DEVELOPMENT OF THE GAZE CONTROL SYSTEM – BENCHTOP TRIAL	114
7.1 BACKGROUND.....	114
7.2 DEVELOPMENT OF GAZE CONTROL SYSTEM.....	116
7.3 BENCHTOP TRIAL STUDY DESIGN	125
7.4 RESULTS	131
7.5 DISCUSSION	136
7.6 CONCLUSION	137
8. IGAZE2.....	138

8.1 BACKGROUND.....	138
8.2 METHODOLOGY.....	139
8.3 RESULTS	148
8.4 DISCUSSION	150
8.5 CONCLUSION	151
9. IGAZE2 – HUMAN TRIAL.....	152
9.1 BACKGROUND.....	152
9.2 METHODOLOGY.....	153
9.3 RESULTS	157
9.4 DISCUSSION	159
9.5 CONCLUSION	161
10. MAIN THESIS OUTCOMES AND FUTURE DIRECTIONS	162
10.1 MAIN OUTCOME OF THIS THESIS	162
10.2 FUTURE PERSPECTIVES.....	164
10.3 CONCLUSION	165
11. REFERENCES	166
12. APPENDICES	194

Figures

Figure 2.1 Human Image Processing	18
Figure 2.2 Adenoma – Carcinoma sequence	21
Figure 2.3 Evolution of the endoscope.	22
Figure 2.4 Image capture via a charge-coupled device of the endoscopic view	23
Figure 2.5 Endorings (Left) and EndoCuff Vision (Right)	25
Figure 2.6 Tobii pro glasses 3 (TOBII, Stockholm, Sweden)- eye tracking glasses	26
Figure 2.7 Example of a scan-path during use of a gaze-contingent keyboard	27
Figure 2.8 Study Selection Flowchart	28
Figure 2.9 Positive correlation between fixation frequency in peripheries versus total procedure weighted score	29
Figure 2.10(Left) – user wearing eye tracking glasses observing withdrawal video, (Right) – Hepatic flexure on left side of screen.	30
Figure 2.11 Left – experimental setup using simulator and fixed camera.....	32
Figure 2.12 Gaze plot of expert (red spots) and non- expert (yellow spots).	35
Figure 3.1 PRISMA (Preferred reporting items for systematic reviews and meta-analyses) flow diagram for study selection.	44
Figure 3.2 Pooled analysis of mean diminutive polyp per patient in CADe vs. conventional colonoscopy groups	48
Figure 3.3 Pooled analysis of mean diminutive adenoma per patient in CADe vs. conventional colonoscopy groups.	49
Figure 3.4 Pooled analysis of mean non-pedunculated polyp per patient in CADe vs. conventional colonoscopy groups	50
Figure 3.5 Pooled analysis of mean non-pedunculated adenoma per patient in CADe vs. conventional colonoscopy groups	51
Figure 3.6 Pooled analysis of mean proximal polyps per patient in CADe vs. conventional colonoscopy groups.	52
Figure 3.7 Pooled analysis of mean proximal adenomas per patient in CADe vs. conventional colonoscopy groups.	53
Figure 4.1 SCOPEPILOT (Pentax, Tokyo)	59
Figure 4.2 Sydney Protocol Biopsy Targets	61
Figure 4.3 Image of mid oesophagus with anterior oesophagus corresponding to “D”	64
Figure 4.4 Image of mid gastric body with anterior stomach corresponding to “D”	64
Figure 4.5 Image of the first part of the duodenum with the anterior duodenum corresponding to “D”	65
Figure 4.6 Image of the second part of the duodenum with the posterior duodenum corresponding to “C”	65
Figure 5.1 STERIS (Mentor, Ohio, USA) range of forceps.	73
Figure 5.2 Range of endoscopic snares	74
Figure 5.3 Endoscopic Mucosal Resection Techniques (lift with hot and cold snare, and underwater EMR).....	76
Figure 5.4 ESD technique	77
Figure 5.5 Knives used in endoscopic submucosal dissection	81
Figure 5.6 Distal attachments	84
Figure 5.7 Haemostasis devices	87
Figure 6.1 Evolution of the endoscope.	Error! Bookmark not defined.

Figure 6.2 Endoscope divided into connection section, control section and insertion tube (left to right)	92
Figure 6.3 Internals of the insertion tube	93
Figure 6.4 Variable stiffness control in an endoscope	94
Figure 6.5 Endoscope Control Section	94
Figure 6.6 Bending section of endoscope with angulation knobs and wires	95
Figure 6.7 Antagonist cables running from steering wheel to endoscope tip	96
Figure 6.8 anticlockwise rotation of the big knob (left) and clockwise (right) producing tip deflection up and down respectively.	96
Figure 6.9 anticlockwise rotation of the small knob (left) and clockwise (right) producing tip deflection left and right respectively.	97
Figure 6.10 Power Spiral (Olympus corp., Japan)	99
Figure 6.11 Aer-O-Scope (GI View Ltd, Israel)	100
Figure 6.12 Endotics (Era Endoscopy, Italy)	102
Figure 6.13 Invendoscope (Ambu, Denmark)	103
Figure 6.14 Endoluminal Assistant for Surgical Endoscopy (EASE) (ICube laboratory, France) (257)	104
Figure 6.15 I ² Snake (Hamlyn Centre, London)	105
Figure 6.16 Master (EndoMASTER Pte, Singapore)	106
Figure 6.17 Flex Colorectal Drive (Medrobotics, Corp, United States)	107
Figure 6.18 Cyclops (Hamlyn Centre, London)	109
Figure 6.19 Meshworm	111
Figure 7.1 Anatomy of endoscope steering with angulation wires	116
Figure 7.2 Dyanmixel Motor (Robotis Techsupport)	117
Figure 7.3 USB DYNAMIXEL motor driver, driving 3 motors connected in series from computer	117
Figure 7.4 Motorised System showing Universal Robotics UR5 arm and motorised printed gears	118
Figure 7.5 Gaze Steering: $r(t)$ = reference point, $y(t)$ = control/ centre of monitor, $e(t)$ = error signal	119
Figure 7.6 Closed Loop Logic	120
Figure 7.7 Gaze Rotation in neutral Position: $r(t)$ = reference point, $y(t)$ = horizontal control ..	121
Figure 7.8 Gaze Rotation	121
Figure 7.9 Setup of System and Benchtop Trial with Task 2	123
Figure 7.10 Monitor display with corresponding arrow showing direction of steering.	124
Figure 7.11 Setup of Task 1 with enclosed spherical phantom (left), internal views (right)	126
Figure 7.12 Setup of Task 2 with head model top left, oropharynx top right, oesophagus bottom left and stomach bottom right.	127
Figure 7.13 NASA-TLX questions	128
Figure 7.14 Ergonomics Questionnaire	129
Figure 7.15 Graph showing Time Taken to Complete each Task by Both Groups	132
Figure 7.16 Top - NASA TLX score for Gaze Control (GC) and Hand Control (HC). Bottom – NASA TLX scores as a percentage extending out, by domain (clockwise)	133
Figure 7.17 Top Van Der Laan acceptance Scores. Bottom – Van Der Laan Acceptance Score by Domain with higher scores at a greater radius.	134

Figure 7.18 Top - Ergonomic Scores as a percentage of respondents for endoscopists for gaze control. Bottom- Ergonomic Scores as a percentage of respondents for non-endoscopists for gaze control.	135
Figure 8.1 Original Eye Gaze steering wheel mount (left) and robotised arm (right).	139
Figure 8.2 Eye Gaze steering wheel mount with thinner steering wheel.	140
Figure 8.3 Eye Gaze steering wheel mount with thicker steering wheel and side to side mount (left) and in use (right).	141
Figure 8.4 Eye Gaze steering wheel mount with rear attachment from three angles.	141
Figure 8.5 Endoscope with iGAZE2 system partially mounted for intubation (left) and with wheel and belts attached (right).	142
Figure 8.6 Foot pedal used to control retroflexion with two additional unmapped pedals.	143
Figure 8.7 Calibration over 20 seconds (left) and 60 seconds (right).	144
Figure 8.8 Anatomical stomach with box removed (left), monitor view of stomach model with targets with central target which number must be placed in(right)	146
Figure 8.9 Task completion time in seconds of iGAZE2 versus Conventional (with standard deviations).	148
Figure 8.10 Retroflexion time in seconds of iGAZE2 versus Conventional (with standard deviations).	148
Figure 8.11 NASA TLX score of iGAZE2 versus Conventional (with standard deviations).	149
Figure 8.12 Radar Plot of NASA TLX subdomains of iGAZE2 versus Conventional (with standard deviations).	149
Figure 9.1 Left – Room Setup without patient or endoscopist, Right – setup with endoscopist and patient (not shown)	153
Figure 9.2 Room Setup showing bed position relative to endoscopist’s seat.	154
Figure 9.3 Left – retroflexion using the iGAZE2 system (patient 2), Right – D1 intubation using the iGAZE2 system (patient 3).	157

Tables

Table 3.1 Quality Assessment - Assessment of bias for RCTs using the Jadad scale; score ≥ 3 = good quality.	45
Table 3.2 Study characteristics of included papers	47
Table 3.3 Summary of CADe (computer-aided detection) versus control.....	47
Table 3.4 Summary of CADe (computer-aided detection versus control for polyp and adenoma detection.	54
Table 4.1 Demographics of survey respondents	67
Table 4.2 Correct responses by total respondents – percentage and absolute number.....	68
Table 4.3 Correct responses: expert endoscopists versus novice endoscopists – percentage and absolute number.	68
Table 5.1 A comparison of ESD knives and their functionalities.....	83
Table 7.1 Time taken to complete tasks with each system by both groups.....	131
Table 9.1 Table showing success of intubation, retroflexion and intervention (where applicable).	158
Table 9.2 Table showing total time and time of system attachment in each patient.	158
Table 9.3 Table showing pain score and medication dosing with ages of patients..	158

1. Introduction

1.1 Prologue

The role of endoscopy in the detection and resection of precancerous and cancerous lesions is well established. The worldwide burden of gastrointestinal cancer continues to increase. There has been continual research work in the last few decades to optimise endoscopy's role in tackling this.

A better understanding of the cancer pathways and precursor lesions has allowed endoscopists to detect lesions earlier. Accordingly, endoscope imaging technology has improved to facilitate lesion detection.

Endoscopy was previously limited to simple lesion resection, but the therapeutic remit has significantly grown with endoscopists now able to resect more advanced lesions with organ saving procedures. The endoscopic therapeutic catalogue has deepened but procedures are still dependent on the ability of endoscopists to perform complex therapy through the conventional endoscope, that remains similar in design since its inception 50 years ago.

The role of vision and endoscopist gaze is an exciting and recent area of research. The combination of this with robotic control systems provides a novel and untouched area of endoscopy research.

1.2 Aims of this Research

The aims of this research are to investigate the role of vision and gaze in endoscopic lesion detection and orientation, the challenges of the current endoscope control system and the potential of combining gaze technology and robotics to provide a novel endoscopic control system.

The aims of this thesis are delivered through three sections. Firstly, the role of vision and gaze in endoscopic lesion detection and localisation is presented including an assessment of endoscopist orientation, the real-world application of AI and the emerging field of gaze analysis in endoscopy. The second section focuses on therapeutic endoscopy, the challenges of the control system, the adjuncts available and the emerging field of robotic endoscopy. The last section combines learning from vision and gaze technologies and robotic control systems to produce and present a novel gaze-controlled endoscope.

1.3 Hypothesis

“The development of a gaze controlled endoscopic system is feasible. A gaze control system is more intuitive than a conventionally controlled endoscope”

The aims of this research and strategies to achieve the aims were:

Investigate the role of vision and gaze in endoscopic lesion detection:

By reviewing the role of lesion detection in endoscopy (Chapter 2)

By systematically reviewing gaze analysis literature in endoscopy (Chapter 2)

By examining endoscopist’s ability to orient themselves during endoscopy (Chapter 3)

By systematically comparing Computer Aided Diagnostic Endoscopy to conventional endoscopy in polyp and adenoma detection rate (Chapter 4)

By systematically comparing Computer Aided Diagnostic Endoscopy to conventional endoscopy in diminutive, sessile and proximal lesion detection rate (Chapter 4)

Investigate the current endoscopic control system:

By reviewing the current endoscope control system and its challenges (Chapter 5)

By systematically reviewing the available endoscopic instruments for advanced therapy (Chapter 5)

By systematically reviewing the current robotic endoscopic control platforms (Chapter 6)

Evaluating a novel gaze controlled robotic endoscope:

By developing a gaze-controlled endoscope system (Chapter 7)

By assessing the feasibility of a gaze control system (Chapter 7 & 8)

By comparing the intuitiveness of an upgraded gaze control system to conventional endoscopy (Chapter 8)

1.4 Thesis Overview

Chapter 2 outlines the role of endoscopy in lesion detection. In the UGI tract early detection of precursor lesions such as Barret's and Chronic Atrophic Gastritis (CAG) reduces progression to cancer. Accurate localisation and orientation of this lesions, for example the intragastric extent of CAG allow appropriate screening and early intervention for such patients. In the LGI tract the adenoma-carcinoma sequence is well established with adenoma detection and resection proven to reduce colorectal cancer risk. Imaging technologies including optical filters and magnification alongside attachable endoscopy devices improve lesion detection. Gaze analysis research in endoscopy shows improved visual search patterns to improve lesion detection and provides a novel and more accurate objective assessment tool of new imaging technologies.

Artificial Intelligence is revolutionising multiple disciplines across Science and Medicine. Computer aided diagnostic endoscopy is one important application of AI and offers potential improvement in lesion detection and thus reduction in GI cancer risk. Chapter 3 systematically reviews CAdE systems in real life use versus conventional endoscopy in both overall polyp and adenoma detection rate, and the most commonly missed polyps and adenomas (sessile, proximal, and diminutive).

Accurate orientation in endoscopy is key to appropriately risk stratify lesions that are detected during endoscopy and plan appropriate interventions. Although much work has been done on the endoscope imaging technology itself there was no research on endoscopist's ability to localise and orient themselves. Chapter 4 presents a trial of endoscopists and their ability to orient themselves in the UGI tract.

The range of endoscopically detected lesions amenable to endoscopic resection has dramatically increased over the last decades. Endoscopic submucosal dissection (ESD) is increasingly the preferred resection method of larger or complex lesions avoiding surgery, and with improved complete resection and reduced recurrence versus endoscopic mucosal resection. Chapter 5 outlines the role of endoscopy in lesion resection and systematically reviews the available ESD tools and the relevant comparative trials. The endoscope control system has remained similar for several decades despite the increasing therapeutic remit. Chapter 6 presents the challenges of the current endoscope control system and reviews the robotic control systems emerging which are all bimanually operated.

Gaze analysis had been only used as a research tool to study endoscopists gaze patterns. The precision movements required of therapeutic endoscopists are compromised by the current control system and the available robotic control platforms still require bimanual control. Chapter 7 presents the novel development of a non-manual endoscopic control platform using gaze as a non-manual control input. The feasibility in a benchtop study is reported. Multiple modifications to the system were made based on the benchtop trial. The intuitiveness of the updated platform is compared to a conventional endoscope in chapter 8.

Chapter 9 presents evaluation of the system in a human trial.

1.5 The Original Contributions of this Thesis

The original contributions of this thesis are:

Comparing the adenoma and polyp detection rate in CADe versus conventional systems in real time CADe use

Comparing the mean diminutive, sessile and proximal polyp, and adenoma per patient in CADe versus conventional systems in real time CADe use

Assessing the ability of endoscopists to orient and localise themselves within the UGI tract

The development of a non-manual gaze controlled robotic endoscope platform

The development of a uni-manual retrofittable gaze controlled robotic endoscope platform

1.6 Publications Arising from Thesis

Sivananthan A et al. Eye tracking technology in endoscopy: Looking to the future. *Dig Endosc.* 2023;35(3):314-322. doi:10.1111/den.14461

Sivananthan A et al. Does computer-aided diagnostic endoscopy improve the detection of commonly missed polyps? A meta-analysis. *Clin Endosc.* 2022;55(3):355-364. doi:10.5946/ce.2021.228

Sivananthan A et al. Orientation in upper gastrointestinal endoscopy-the only way is up. *World J Gastrointest Endosc.* 2023;15(3):146-152. doi:10.4253/wjge.v15.i3.146

Sivananthan A et al. The evolution of lower gastrointestinal endoscopy: where are we now?. *Ther Adv Gastrointest Endosc.* 2020;13:2631774520979591. Published 2020 Dec 20. doi:10.1177/2631774520979591

Sivananthan A et al. Endoscopic submucosal dissection: an update on tools and accessories. *Ther Adv Gastrointest Endosc.* 2020;13:2631774520957220. Published 2020 Sep 28. doi:10.1177/2631774520957220

Sivananthan A et al. A novel gaze-controlled flexible robotized endoscope; preliminary trial and report. *Surg Endosc.* 2021;35(8):4890-4899. doi:10.1007/s00464-021-08556-1

Sivananthan A, et al. Gaze Controlled Endoscopy. *Surgical Life* 2021, 59: 28-31

Sivananthan A et al. Eye-controlled endoscopy - a benchtop trial of a novel robotic steering platform - iGAZE2. *J Robot Surg.* 2024;18(1):266. Published 2024 Jun 25. doi:10.1007/s11701-024-02022-5

1.7 Posters Arising from Thesis

Sivananthan, A et al. Performance of Computer Aided Detection Systems in Flat, Sessile and Diminutive Adenomas: A Meta-analysis. Digestive Diseases Week 2021 (Virtual).

Sivananthan, A et al. Eye Controlled Endoscopy – A Benchtop Trial of a Novel Robotic System. Poster Presentation. DDW 2023 Chicago

2. Endoscopic Lesion Detection: A Review of Gaze Analysis in Endoscopy

Content from this Chapter was Published in (1):

Sivananthan A et al. Eye tracking technology in endoscopy: Looking to the future. *Dig Endosc.* 2023;35(3):314-322. doi:10.1111/den.14461

2.1 Background:

The incidence of gastrointestinal cancer continues to rise globally. Diagnostic endoscopy is critical not just in identifying cancerous lesions but pre-cancerous lesions also. Endoscopy programmes have been rolled out globally with successful decrease in cancer incidence and mortality. Early diagnosis of pre-cancerous pathology in the gastrointestinal tract allows appropriate surveillance of lesions or earlier treatment of lesions with lower risk interventions and reduced risk of recurrence. The success of endoscopists to detect these lesions are reliant on the endoscope imaging technology and available enhancements to improve detection.

Orientation in endoscopy is not previously described but can be derived from existing understanding of spatial orientation (2). Orientation in endoscopy is predominantly reliant on two main sensory inputs: visual and vestibular.

Images from the camera in the endoscope tip through fibreoptics and image processing are displayed on the endoscope monitor. Light from the monitor passes through the endoscopist's pupils and is refracted through the lens towards the retina. Here rod and cone photoreceptors convert the light energy into action potentials which are transmitted via the optic nerve to the visual cortex situated in the occipital lobe (Figure 2.1).

Alongside the visual inputs, proprioception from the endoscope control system plays a key role in endoscopic orientation. Proprioceptive sensory receptors in the muscles, tendons and joints

transmits information including joint position sense, sense of force, sense of change in velocity and kinaesthesia (the awareness of motion).

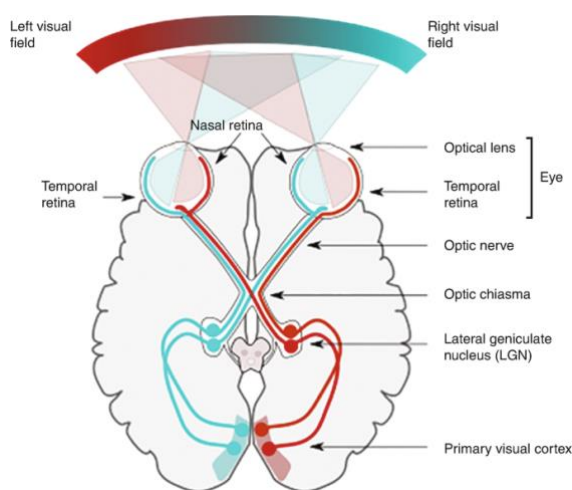


Figure 2.1 Human Image Processing

Complex interconnection between these sensory modalities allows the endoscopist to orient themselves using the visual input of the endoscope monitor and the hand position on the endoscope and endoscope wheels. This is combined with endoscopist's learned reference points for example the understanding of intraluminal anatomy to understand the current location of the endoscope and the movements required to move the endoscope to a desired location.

In this chapter the diagnostic role in upper gastrointestinal (UGI) and lower gastrointestinal detection (LGI) and the natural history of upper gastrointestinal and lower gastrointestinal cancerous lesions are presented. The imaging system of an endoscope is then reviewed followed by a systematic review of the novel use of eye tracking technology to improve endoscopic lesion detection.

The aims of this chapter are to:

1. To outline the role of endoscopy in lesion detection
2. To review imaging technologies and adjuncts to improve detection
3. To review the role of gaze analysis research applicable to endoscopic detection

2.2 The Role of Endoscopy in Lesion Detection

2.2.1 Upper Gastrointestinal Cancer Screening

Upper Gastrointestinal Cancer makes up a significant burden of global cancer incidence and mortality. Successful endoscopic identification of cancer with appropriate surveillance is critical to reducing cancer burden and mortality. There are no validated serological or non-invasive markers to identify precancerous or cancerous gastrointestinal (GI) pathologies and endoscopy remains the main tool for diagnosis. Post Endoscopic Upper GI Cancer (PEUGIC) is a devastating outcome after an endoscopy defined as an UGI cancer diagnosed 6-36 months after nondiagnostic endoscopy. A recent UK analysis suggested that 42.6% of PEUGIC can be attributed to a missed lesion during endoscopy (3).

2.2.1.1 Oesophageal Cancer

The burden of oesophageal cancer is reducing globally (4) but in Western countries appears to be increasing. It is the 7th most common global cancer with an incidence of 500,000 new cases annually. Oesophageal cancer has a devastating mortality impact with a 5-year survival rate under 20% (5) with 500,000 deaths annually. The most common subtypes are adenocarcinoma (most common in the developing world) and squamous cell carcinoma (more associated with the Western world) (6). There is an increasing burden of squamous cell carcinoma attributable to increasing obesity and reflux disease (7–9). Barrett's oesophagus is an important and well recognised precursor lesion to adenocarcinoma. Reflux of gastric contents causes distal oesophageal mucosal metaplasia of squamous epithelium to columnar epithelium which is a precancerous lesion. Identification of Barrett's oesophagus allows risk stratification of the Barrett's oesophagus through both histological macroscopic assessments. Pending this, patients will enter a surveillance programme to identify high grade dysplasia or early (intramucosal) cancer which in many cases can undergo endoscopic therapy such as radiofrequency ablation, or endoscopic or surgical resection (10).

2.2.1.2 Gastric Cancer

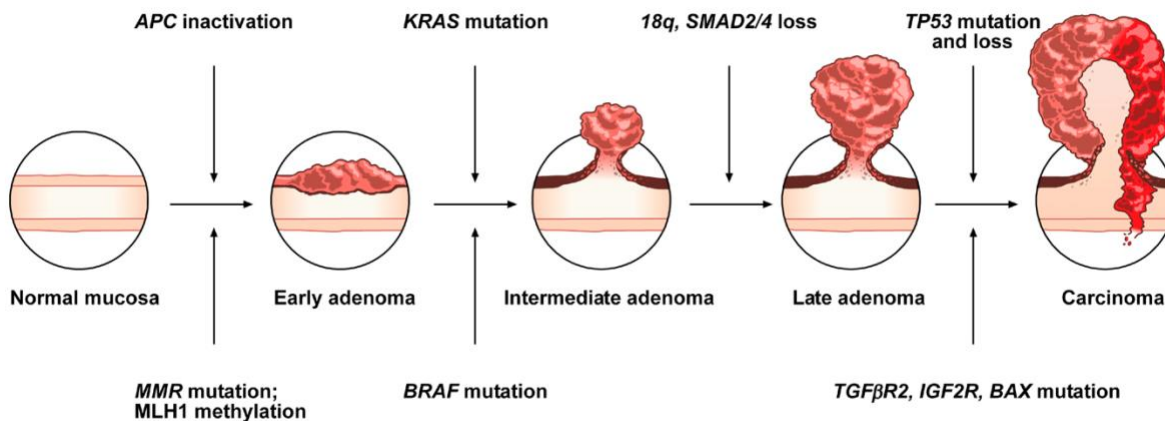
Gastric cancer is the 5th most common cancer globally (11). There are 1.1 million annual cases with 770,000 annual deaths (12). The global 5-year survival rate of gastric cancer is 29% (13). Chronic atrophic gastritis is a key precursor lesion to gastric adenocarcinoma. Chronic atrophic gastritis includes both gastric atrophy (GA) (loss of glandular cells with a chronic inflammatory mucosal infiltrate) and gastric intestinal metaplasia (GIM) (replacement of epithelial glandular cells small bowel intestinal type cells). Gastric low grade and high-grade dysplasia also represents a key precursor lesion.

Endoscopic identification of GA, GIM or dysplasia allows patients to undergo appropriate surveillance or treatment. GA confers a 1.9% 5-year risk of gastric cancer, GIM 5.3 – 9.8%, low grade dysplasia 0-23% and high grade dysplasia 60-85% (14). If chronic atrophic gastritis is identified on endoscopy a combination of image enhanced endoscopic examination and Sydney protocol biopsies allow appropriate risk stratification and thus appropriate surveillance or treatment. The Sydney protocol requires separate biopsies of the gastric antrum, incisura, lesser curve and greater curve. Extent of atrophy i.e. the involvement of the lesser and greater curve and extent beyond the antrum into the body, correlates with the risk of gastric adenocarcinoma (15,16). This requires accurate endoscopic orientation and anatomical localisation to appropriately risk stratify atrophic gastritis.

2.2.2 Lower Gastrointestinal Cancer Screening

Colorectal cancer continues to increase in prevalence. Currently colorectal cancer represents 10.2% of all cancers worldwide (17) and is predicted to expand to 2.2 million cases and 1.1 million deaths by 2030 (18). Most colorectal cancers are adenocarcinoma evolved from adenomas via the well-established adenoma-carcinoma sequence (Figure 2.1).

CIN - Chromosomal Instability pathway



MSI - Microsatellite Instability pathway

Figure 2.2 Adenoma – Carcinoma sequence

Colonoscopy allows identification and removal of colonic adenomas preventing progression to cancer (19). An increase in detection of adenomas by 1% reduces the risk of colorectal cancer by 3% (20).

Lesions are classified by morphology and size. The Paris classification system is most commonly used to describe the lesion morphology. Dependent on the morphology and size of the lesion further interrogation of the lesions can also be undertaken by use of a variety of imaging technologies and classification systems. The main purpose of this is to firstly predict the histology of the lesion and thus gain an understanding of the ongoing risk of this lesion and to estimate the risk of submucosal invasion and thus the appropriateness of endoscopic resection techniques. There are many visual classification systems used to estimate histology and invasion which include Kudo-Pitt pattern and Japan NBI Expert Team (JNET) classification. National colonoscopy screening programmes play an important role in the prevention of colorectal cancer. Case control studies have demonstrated a reduction in 10 year colorectal cancer risk in both Germany and the USA (21,22). Cancer diagnosed after a “negative” colonoscopy is known as post colonoscopy colorectal cancer (PCCRC). A single-centre retrospective study carried out over an eight year period, found that 85 per cent of PCCRC was due to missed lesions during colonoscopy(23).

2.3 Imaging in Endoscopy

Bozzini first developed the candle and mirror illuminated “Lichtleiter” endoscope in 1806 (24). Edison’s incandescent bulb allowed better illumination which Mikulicz used in the tip of his gastroscope in 1881 (25). The introduction of fibreoptic technology allowed non-linear transmission of images enabling Hirsschowitz to present the first fully flexible “fibrescope” at the American Gastric Annual Meeting in 1957 (26). Miniaturisation of a charged couple device allowed Welch Allyn to release the first video endoscope in 1983 closely resembling the endoscope we are familiar with today (27) (Figure 2.2).



Figure 2.3 Evolution of the endoscope.

A) Lichtleiter Endoscope (1806), B) Mikulicz Gastroscope (1881) C) Schindler's Gastroscope (1932) and D) Hirsschowitz fibrescope (1957)

Illumination in the current endoscope is provided by fibreoptic cables which can transmit light from the external light source through illumination fibres to the endoscope tip and thus the gastrointestinal mucosa. Light is then shone on the mucosa and reflected at the lens.

The charged couple device was an instrumental technology in allowing the transmission of undistorted high-quality images in a cheap and effective way (Figure 2.3). The image reflected back is captured by a sensor made up of silicon wafers divided into tiny sections known as pixels. The powerful xenon light is transmitted to the mucosa via fibreoptic cables. The reflected light from the mucosa is made up of photons. These photons are captured by the light sensitive elements. Photons are converted into electrons i.e. an electric signal by the charge coupled device. The strength of the electric signal is proportional to the brightness of the reflected light.

To allow colour differentiation the pixels are divided into a random array of red, green, and blue light filtered sensors. This allows accurate approximation of the colour signal of each pixel without any meaningful compromise to the image detectable by the human eye. This proves to be significantly cheaper and more efficient than using a separate charge couple device for red, green, and blue.

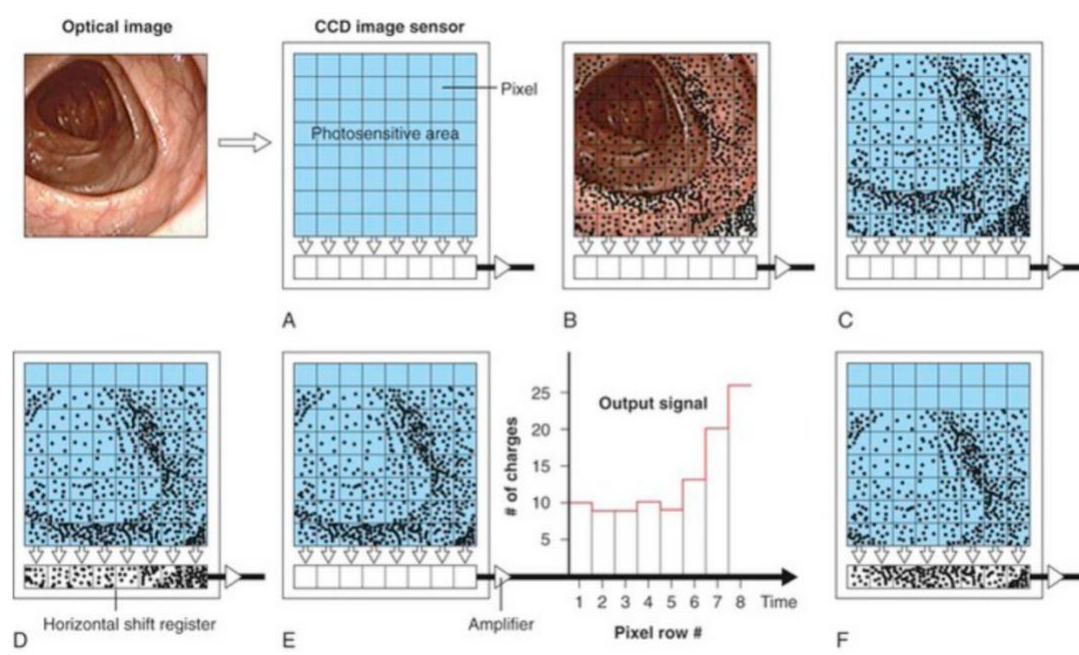


Figure 2.4 Image capture via a charge-coupled device of the endoscopic view

This electrical signal is then transmitted via wires through the endoscope to the external video system and then converted to an image presented on the endoscope monitor.

Imaging Technologies

High-Definition White Light Endoscopy and magnification has allowed ever more detailed mucosal assessment. Endocytoscopy is a commercially available magnification technology allowing cellular level vision at 1000 times magnification. Wide angled endoscope allow a greater mucosal coverage to improve diagnostic yield.

Optical filters and post processing of images has allowed even greater differentiation of lesions than white light allows. Technologies include narrow band imaging (Olympus, Japan), 'I-Scan' (Pentax, Japan), FICE (Fujinon, Japan), blue laser imaging endoscopy (Fujinon, Japan) and linked colour-imaging (Fujinon, Japan) (28). These technologies have shown significant improvements in adenoma detection rate (ADR) and have been incorporated into the everyday practice of many endoscopists.

Further technologies such as optical coherence tomography, confocal laser endomicroscopy, elastic scattering spectroscopy, autofluorescence imaging and endoscopic polarized scanning spectroscopy may move us closer to optical rather than histological diagnosis but these are predominantly research techniques currently.

Accurate optical diagnosis would allow a resect and discard approach of diminutive lesions with attractive potential cost savings. A simulated model of such a strategy in the USA suggested \$33million of annual savings (29) which projected worldwide would have significant global cost saving implications.

Lower Gastrointestinal Detection Adjuncts

Attachable devices such as Endocuff (Arc Medical Ltd., Leeds, UK) and purpose-built scopes such as G-Eye™ (Pentax Medical, Tokyo, Japan) improve mucosal visualisation by mechanically opening up haustral folds on withdrawal. EndoCuff, shown in Figure 2.4, is a disposable plastic cap that is attached to the endoscope tip with plastic soft branches that extend on withdrawal, holding colonic folds open. Evidence has been mixed with some meta-analyses showing improved ADR (41.3% vs 34.2%(30), RR 1.18 (31), OR 1.37 (32)). The prospective randomised control trial (ADENOMA TRIAL) showed an ADR of 40.9% vs 36.2% in the bowel cancer screening programme(33) however a prospective Randomised Control Trial in bowel scope patients (B-Adenoma (34)) showed no improvement versus conventional endoscopy (35).

A recent systematic review and meta-analysis looking at “behind fold visualising techniques” including cap assisted, Endocuff vision, Endorings and FUSE showed no improvement in ADR

versus conventional colonoscopy although there was a significant improvement with G-Eye (Pentax, Japan) with a relative risk of 1.3 (36).

Although colonoscopy remains the gold standard for investigation of the colon there are those who are unable to tolerate complete optical colonoscopy. Other options for luminal screening include CT colonography and colon capsule endoscopy. Colon capsule endoscopy, with the second generation PillCamTM2, involves swallowing a less than 3 gram capsule which wirelessly transmits data to an external recorder worn by the patient (37). It is a safe and well tolerated examination (38). This second generation device has sensitivities for polyps greater than 5mm in size, approaching that of optical colonoscopy but comparison to CT colonography is less clear with conflicting recent evidence (39).

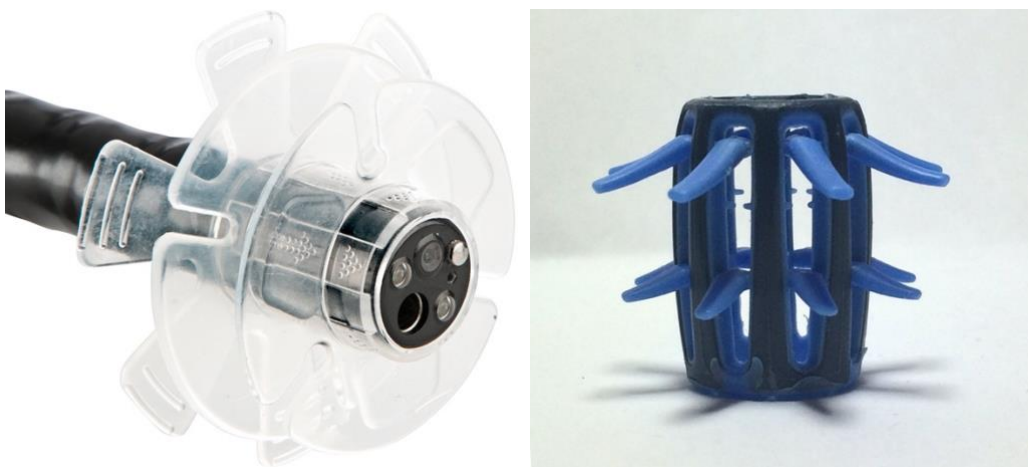


Figure 2.5 Endorings (Left) and EndoCuff Vision (Right)

2.4 Gaze Analysis in Endoscopy

The detection of gastrointestinal luminal endoscopic lesions greatly relies on the visual gaze patterns of endoscopists. Eye tracking and gaze analysis offers valuable insight into the differences in visual patterns between highly skilled experts and novice endoscopists. As the tools required Video-oculography (VOG) have become cheaper, an evolving evidence base of gaze analysis in endoscopy is developing.

This section presents a systematic review of all available evidence of gaze analysis in gastrointestinal endoscopy.

2.4.1 Eye tracking in Endoscopy

Eye tracking is the real time assessment of the horizontal, vertical, and occasionally torsional movements of both eyes. Eye tracking evolved from simple observation by the scientist to contact methods of eye tracking. Electro-oculography uses electrodes placed around the eye to measure the change in electrical potential when the eye moves towards an electrode (as the retinal pigment epithelium generates an electrical current). Scleral contact lenses use soft contact lens with electrical coils that generate electrical currents as they move through an electro-magnetic field(40).

Video-oculography (VOG) is a non-contact method of eye tracking that has made it significantly more accessible and cheaper for research. VOG can be performed by a stationary camera recording eye movements or eye tracking glasses worn by the user (Figure 2.5) (41).



Figure 2.6 Tobii pro glasses 3 (TOBII, Stockholm, Sweden)- eye tracking glasses

2.4.2 Gaze Analysis in Medicine

Gaze analysis has been utilised successfully in other areas of medicine. In the field of neuropsychiatry, the analysis of eye movements, specifically during tasks like saccades, smooth pursuit, and visual search, can be used to diagnose conditions such as schizophrenia (42), Parkinson's disease, and Attention Deficit Hyperactivity Disorder (43).

Furthermore, eye movements can have therapeutic applications. By utilizing eye tracking glasses, eye movements can be used as a control input. Gaze movement direction can be used similarly to manual control of a joystick, and this is known as "gaze control". Therapeutic use of gaze control has been effective in improving communication in those with "locked in syndrome" (44) allowing them to communicate through gaze control interfacing with a virtual keyboard (45) (Figure 2.6) (45). With experience and training users of this system can generate words as up to 20 words a minute significantly improving their ability to communicate.

Figure 2.7 Example of a scan-path during use of a gaze-contingent keyboard

This study utilized the methodology outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Given that this research was a literature review, consent or ethical/institutional review was not necessary. The objective of the literature search was to assess the existing evidence regarding the utilization of eye gaze, gaze analysis, and eye tracking in gastrointestinal endoscopy with the potential to enhance its effectiveness.

Two authors (Arun Sivananthan and Javed Ahmed) participated in the literature search and study selection process. Any disagreements that arose were resolved through discussions involving a third author (Nisha Patel). The inclusion criteria focused on human studies that were relevant to

the research question, peer-reviewed, and published in English. Studies in languages other than English, those deemed irrelevant, and duplicate publications were excluded from the review.

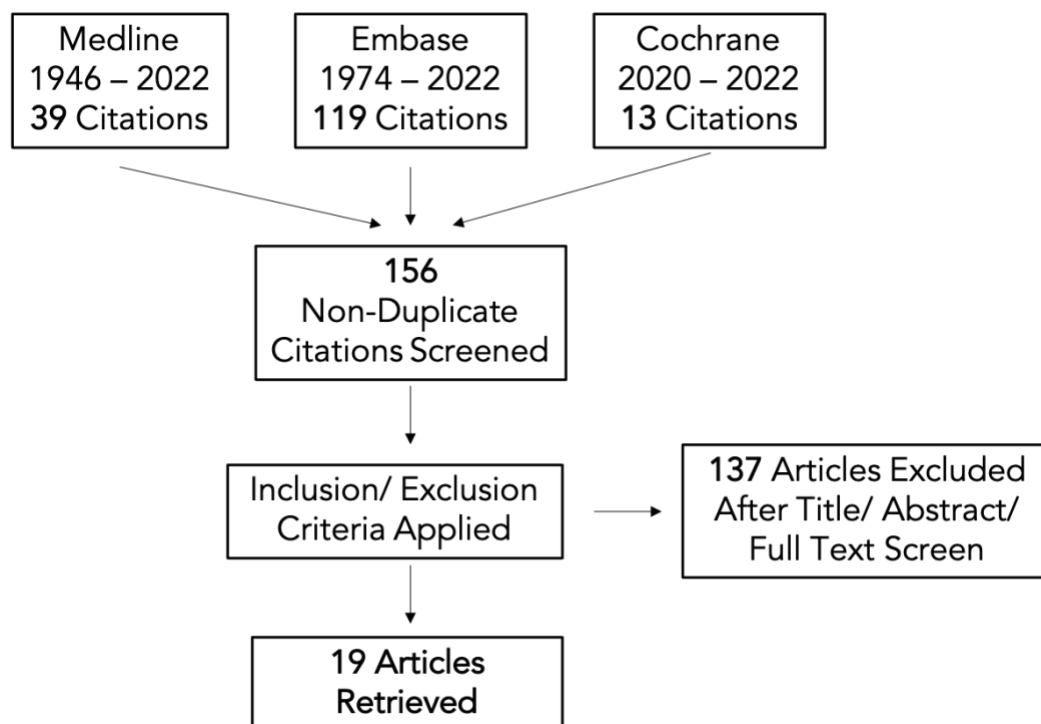


Figure 2.8 Study Selection Flowchart

2.4.4 Review Results

19 eligible studies were identified as detailed in the study selection flow chart (Figure 2.7). The studies were collected into the following themes “visual search strategies for polyp detection”, “keeping a luminal view”, “endoscopy training”, and “objective assessment of lesion detection”.

2.4.4.1 Visual Search Strategies for Polyp Detection

The utilization of visual search strategies plays a significant role in the successful identification of polyps during gastrointestinal endoscopy. Gaze analysis has indicated that increased gaze in the peripheries, both on the endoscopy monitor and within the bowel lumen, is associated with higher lesion detection rates and with experienced endoscopists (46,47).

In a study by Lami et al.(46), the visual search strategies of eighteen endoscopists were examined and correlated with their polyp detection rates. Eye tracking glasses were worn to record gaze during a two-minute withdrawal from the caecum. The study analysed fixations, including the number and duration in each area of interest. Data was correlated both anatomically and by the monitor. In the anatomical analysis the lumen corresponded to the centre with a three-by-three grid around it. In the screen-based analysis the centre was defined as the centre of the monitor. This was analysed against the polyp detection rate of each endoscopist.

The analysis showed that gaze focussed on the outer ring was positively correlated with a higher polyp detection rate. Similarly, a higher PDR was associated a greater number of fixations and longer duration spent in the outer ring both for the anatomical (fixation count $r = 0.56$, $P = 0.02$; fixation time $r = 0.62$, $P < 0.01$) and screen-based analysis (fixation count $r = 0.55$, $P = 0.02$; fixation time $r = 0.56$, $P = 0.02$). Also, it was noted that there was a significant positive correlation between time spent focused on the monitor versus away from the monitor with PDR.

A separate study by the same group analysed the gaze patterns of twelve trainee endoscopists who performed a total of twenty-four colonoscopies. The procedures were objectively scored by an independent assessor using a procedural score developed by the Joint Advisory Group on gastrointestinal endoscopy. This scored the endoscopy between 1 and 20. The results demonstrated a positive correlation between fixation frequency on the outer circle (both lumen and screen) with a higher procedure score (Figure 2.8) (47).

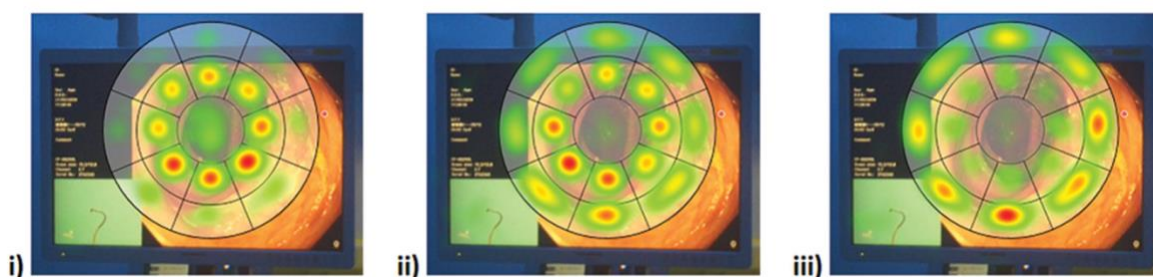


Figure 2.9 Positive correlation between fixation frequency in peripheries versus total procedure weighted score

Heat map shows cumulative fixation distribution. (i) the lowest scoring 8 colonoscopies, (ii) the middle scoring 10 colonoscopies, and (iii) the highest scoring 8 colonoscopies (from bottom left to top right of the graph).

A further trial compared gaze patterns between twenty novice and fourteen experienced endoscopists during the observation of a video depicting withdrawal through the hepatic flexure (Figure 2.9). This showed that experienced endoscopists had a significantly higher percentage of peripheral fixations (13.4% vs 23.0%, $P = 0.013$). Of note they also reported that experienced endoscopists had a significantly greater percentage of left-sided fixations during withdrawal through the hepatic flexure (*18.6% vs 33.5%, $p=0.005$) (48). These findings align with a more active search of the poorly visible left bend of the hepatic flexure by experienced endoscopists.



Figure 2.10(Left) – user wearing eye tracking glasses observing withdrawal video, (Right) – Hepatic flexure on left side of screen.

The studies have not all produced a unifying agreement and of note an older study from 2010 conflicted with the idea that peripheral fixations correspond with a higher quality of endoscopy(49). This was a small, simulated study with 11 endoscopists watching a video of a colonoscopy withdrawal. This study interestingly showed that adenoma detection rate was significantly positively correlated with an increased percentage of fixations in the central section of the screen ($r= 0.67$, $p=0.024$). Similarly, an increased mean gaze time in the central segment of the screen was also positively correlated with ADR ($r= 0.70$, $p=0.017$). It is worth noting the small sample size, older technology, and use of a video as a possible explanation to the conflicting conclusion versus more recent studies.

For example, Patel et al., in a study from 2022, was more favourable of a peripheral search strategy (50). The prospective study by Patel et al. involving 33 endoscopists found a trend of lower total duration of fixations on the central lumen as polyp detection rates increased

Wenzke et al. looked at the evolution of visual gaze patterns over time by a within group comparison over time. First year endoscopy fellows' gaze patterns were compared against their gaze patterns two years later. Over time they demonstrated a higher mean gaze time and fixation numbers in the periphery compared to the centre (51). The mean gaze time and number of fixations were 2-2.53 x higher in the periphery than the centre.

Early work comparing 3 experts and 3 novices watching colonoscopy videos suggested faster eye movement speed in experts than in trainees (33.3 pixels/frame $\pm$ 2.7 vs 26.7 $\pm$ 1.0)($p=0.03$) (52). However, the small sample size must be noted.

Visual gaze patterns in upper gastrointestinal endoscopy have also been studied. A pilot study examined five endoscopists completing 35 OGDs. Experienced endoscopists were defined as having completed more than 1000 endoscopies and novices as having completed less than 1000. Heat maps generated from the endoscopists' gaze patterns suggested that more experienced endoscopists spent more time in "blind spots" such as the greater curvature of the upper part, posterior wall of the body, and lesser curvature of the antrum. However, due to the small sample size, no statistically significant evaluation could be achieved, but it demonstrated the feasibility of visual gaze analysis in identifying the visual gaze patterns of expert endoscopists compared to novices in upper gastrointestinal endoscopy (53).

In summary, these trials indicate that expert endoscopists tend to allocate more visual search time to the peripheries of the screen. They also demonstrate that experts adjust their visual search strategies in poorly visualized areas, such as the hepatic flexure or posterior body of the stomach, unlike novices. It is important to acknowledge that these studies have limited statistical power and employ heterogeneous methodologies, but they provide compelling evidence supporting the effectiveness of improved visual search strategies among experienced endoscopists and the potential of gaze analysis to further understand this.

2.4.4.2 Keeping a Luminal View

A core skill of high-quality endoscopy is to maintain a view of the gastrointestinal lumen allowing complete mucosal examination and thus lesion detection. There are many challenges to

keeping a luminal view including the tortuous nature of the lumen, peristalsis, and mucosal folds.

Gaze analysis was used in a study to identify the different approaches to loss of a luminal view between expert and novice endoscopists(54). Twenty novice endoscopists were compared to six expert endoscopists. All endoscopists completed simulated virtual reality endoscopies whilst wearing eye tracking glasses. The endoscopic image was categorised as bowel lumen in centre of screen (BLC), bowel lumen at edge of screen but visible (BLV) or lumen lost entirely from screen (BLL) (Figure 2.10).

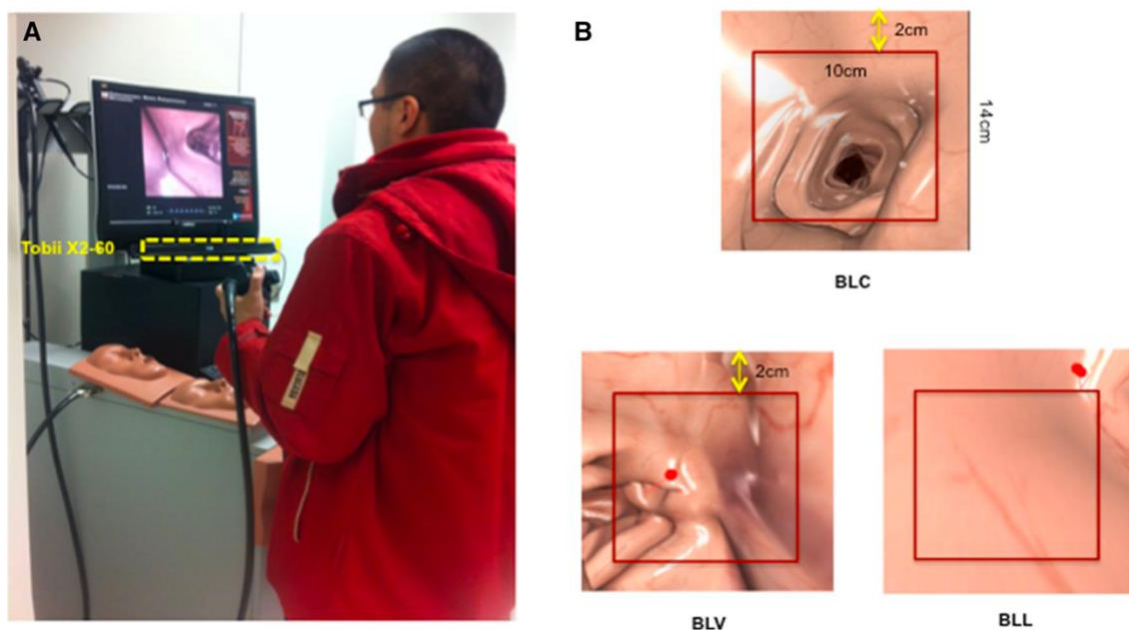


Figure 2.11 Left – experimental setup using simulator and fixed camera.

Right - bowel lumen in the centre of the screen (BLC), bowel lumen at the edge of the screen but visible (BLV) or bowel lumen lost from the screen (BLL) (54).

Each endoscopy was analysed, and the percentage of time spent in each category was recorded. The number of transitions between each category were noted, for example the number of times the view went from the lumen visible at the edge of the screen (BLV) to being entirely lost (BLL). The rate of saccades was also noted.

Expert endoscopists had a significantly higher proportion of the endoscopy with the lumen centred (BLC= 70% vs. 51%, $P = 0.108$). When the lumen was only visible at the side of the screen (BLV), expert endoscopists had a significantly higher number of transitions to the lumen being in the centre of the screen (BLC) versus novices ($n = 7$, 29% vs $n = 125$, 18%, $P < 0.001$). Accordingly, novices were significantly more likely than experts to move from a view with the lumen at the side of the screen (BLV) to a complete loss of the luminal view (BLC) ($n = 61$, 9% vs $n = 0$, 0%).

When the lumen went to the edge of the screen the expert endoscopists displayed a higher saccadic rate than when centred (BLC: 5.81 ± 1.57 counts vs BLV: 4.73 ± 1.31 counts). Novices however had no significant change in saccadic rate when the lumen was at the edge of the screen versus when centred (BLC: 4.08 ± 1.49 counts, BLV 4.20 ± 1.41 counts).

This study suggests that experienced endoscopists are able to spend a higher percentage of the endoscopy with the luminal view centred and when the view is almost lost, they employ a more active visual search strategy to regain the luminal view. This objective insight provides a potentially good objective marker of quality of endoscopy where surrogate and subjective markers are currently relied upon, but further work would be required.

2.4.4.3 Endoscopy Training

Training endoscopists involves significant time investment of coaching, instructing, and mentoring. Endoscopy training elongated procedure times and thus compromises endoscopy units' abilities to meet targets, particularly pertinent in the context of the post pandemic backlog(55).

Gaze analysis has shown to be a potentially useful training support tool when used in combination with AI learning and may potentially replicate some of the training traditionally provided by a trainer.

A trial involving eight novice endoscopists (defined as less than 10 attempted procedures) completed a virtual reality colonoscopy with gaze analysis through eye tracking glasses(56). The

colonoscopy view was analysed, and any losses of luminal view were noted and labelled as “loss of luminal view”.

There were 51 “losses of luminal view” and the gaze patterns including fixation and saccades were recorded during both the navigation loss and subsequent reorientation. This data was then used to train the system using a deep neural network to provide audible alerts at the point of navigation loss. The system had a high accuracy, sensitivity, and specificity (91.80%, 90.91% and 94.12%).

Using this system as a base the group are now developing an automate training algorithm that can deliver instruction at the point of navigation loss to the trainee to re-establish a luminal view. A system like this could be a useful tool to provide training without need for a human trainer. Systems like this could also be beneficial to maintain training of endoscopists even after completion of basic certification.

2.4.4.4 Objective Assessment of Lesion Detection

There are an increasing number of exciting innovations in endoscopic imaging technologies. Many of these are focussed on lesion detection. Objective comparison trials are challenging, and evaluation of endoscopic imaging technologies often relies on subjective reporting of lesion detection. Eye tracking with gaze analysis offers an objective assessment of lesion detection. Gaze can be analysed to show the exact moment a lesion is detected, and the time taken to see a lesion.

This use of gaze analysis was used to compare three different imaging technologies and their relative efficacy in polyp detection (57). Blue laser imaging (BLI) (Fujifilm Co., Tokyo, Japan) uses two lasers (410nm and 450nm) instead of the traditional xenon light with a purported improvement in endoscopic image clarity and thus improve polyp detection. This technology was developed by Fujifilm. Linked Colour Imaging (LCI) (Fujifilm Co., Tokyo, Japan) also developed by Fujifilm is a novel imaging technology that uses a brighter light both pre and post image processing to emphasise slight colour differences in the mucosa and thus also improve lesion detection.

Ten endoscopist reviewed thirty endoscopic images with BLI, LCI and standard white light imaging (WLI). Eye tracking information was captured by a fixed eye tracker attached to the monitor. After gaze analysis the exact time taken from looking at the image and fixating on the lesion was recorded as an objective measure of lesion detection, if indeed the lesion was seen and fixated on. The gaze plots of experts versus non experts were also recorded (Figure 2.11).

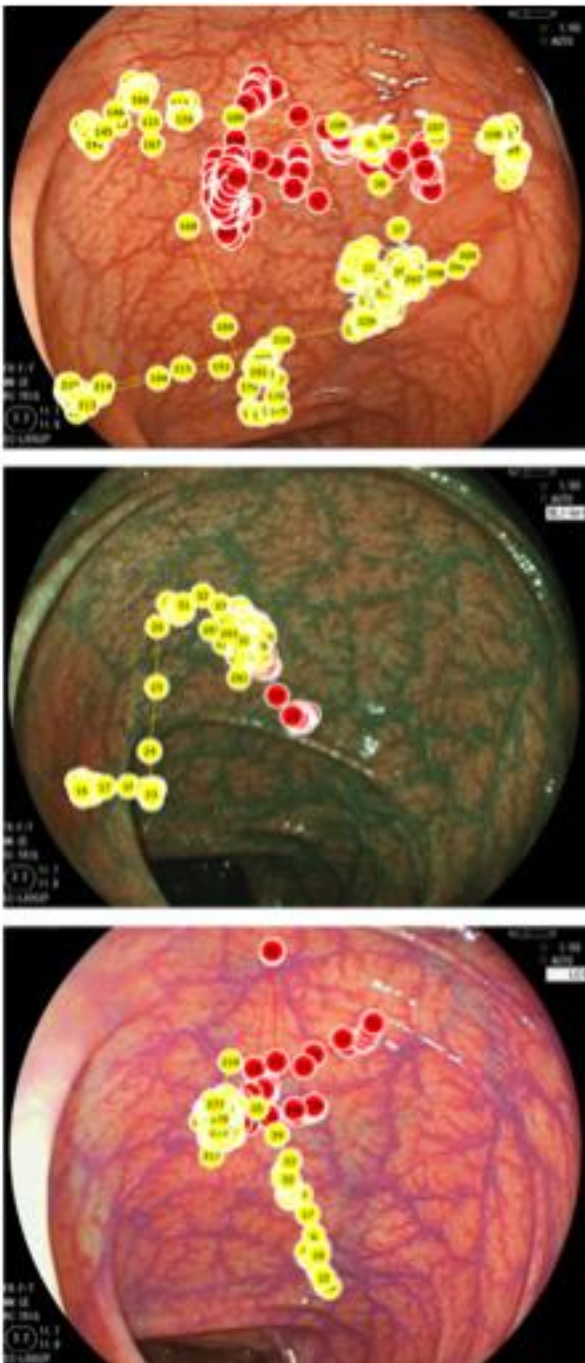


Figure 2.12 Gaze plot of expert (red spots) and non- expert (yellow spots).

White light imaging (top), Blue laser imaging (Middle), Linked-colour imaging (Bottom) (57)

The lesion miss rate with BLI (6.0%) and LCI (4.3%) was significantly lower ($p < 0.01$) than with WLI (12.6%). Mean detection time of lesions with BLI (1.01 ± 1.21 s) and LCI (1.10 ± 1.16 s) was significantly quicker ($p < 0.0001$) than WLI (1.58 ± 1.60 s). There was no significant difference between BLI and LCI. It is well documented that improved lesion detection is directly correlated with lowering colorectal cancer risk. This trial shows an effective use of gaze analysis to objectively assess imaging technologies in this important area of diagnostic endoscopy.

Bleeding is a recognised and important aspect of endoscopic submucosal dissection. Identifying the exact source of bleeding to allow adequate quick and efficient management is vital to this advanced endoscopic procedure. A novel imaging technology, dual red imaging (DRI) using 2 wavelengths of light (600 and 630nm) was proposed as a potential technology to improve the detection of sources of bleeding during endoscopic submucosal dissection (ESD). Gaze analysis was used as an objective analysis tool to compare DRI to WLI endoscopy(58).

Four advanced endoscopists who had completed over 100 ESDs each watched 20 cases of ESD related bleeding with WLI and 20 cases with DRI. Their gaze patterns were analysed from eye tracking glasses and recorded the distance of eye movement for every 20ms thus giving a value of mean eye movement in pixels per unit of time. This demonstrated that mean eye movement distance was significantly lower when using DRI vs WLI. This was the case for all four endoscopists ($3.93 \pm .44$ vs $5.43 \pm .41$ pixels [$P = .0116$], $2.07 \pm .24$ vs $2.92 \pm .22$ pixels [$P = .0081$], $1.53 \pm .23$ vs $2.21 \pm .21$ pixels [$P = .0381$], and $1.47 \pm .23$ vs $2.02 \pm .19$ pixels [$P = .0174$], respectively). The shorter distance of eye gaze to identify the bleeding point with DRI provides an objective and reproducible indicator of the value of DRI in ESD.

Computer Aided Diagnostic Endoscopy (CAdE) is another exciting imaging technology utilising convolutional neural network training to produce a system that can improve adenoma detection as well as other lesions including dysplasia. Visual gaze analysis has been used in three trials to objectively assess CAdE systems.

A trial using 50 video clips and 10 endoscopists was conducted with and without CAdE systems whilst using eye tracking glasses(59). The order of videos and use of CAdE was randomised, and the clips were watched a week apart. Gaze analysis was used to objectively identify when the

lesion was first seen by using the time taken to fixate on the lesion; 'time to first fixation' (TTFF). When using CADe, TTFF was significantly quicker versus than without (0.690.49 s vs. 0.850.62 s; $P<0.01$).

To test the concept of CADe a 'perfect system' was simulated by videos with green boxes placed around polyps(60). A selection of videos was created with and without the 'CADe' system. 9 fellows randomly watched both videos a week apart. Gaze analysis was used to identify the 'time to visualise' (TTV) the polyp and the polyp visualisation rate (PVR). Using the 'perfect system' showed a significantly improved TTV and PVR versus without (0.95s +/- 0.0088s vs 1.53s +/- 0.021s and 93.1% +/- 0.14% vs 81.14% +/- 0.23%) respectively.

Gaze analysis has also been used to trial the GI Genius system (version March 2020, Medtronic GmbH, Meerbusch, Germany), a commercially available CADe system(61). 29 videos with and without the CADe system were shown to 17 endoscopists (including novice endoscopists and expert) whilst wearing eye tracking glasses. 17 videos had single polyps and 12 had false positive detections. There was a three-week gap in between them using each system. This study showed a shorted eye travel distance with the CADe system (232.68cm (99%CI = 210.43–262.33)) vs without (248.86cm (99%CI = 221.39–282.88)) but this was similarly reflected in the videos with false positives detected 329.76cm (99% CI = 293.81–387.00)) vs (368.95cm (99% CI = 331.75 – 395.10)).

Overall, these studies show the feasibility of gaze analysis as an objective tool to assess endoscopy technologies in a reproducible way not reliant on subjective reporting. With the large numbers of innovative tools gaze analysis could provide an effective way to truly assess each tool's value.

2.5 Conclusion

Endoscopy plays a critical role in identifying pre-cancerous and cancerous luminal pathology. UGI and LGI cancer remains a significant global burden with increasing prevalence in Western countries. Surveillance programmes and guidelines enable successful detection of precursor lesions with proven reduction in cancer prevalence and mortality. Endoscopic detection of lesions is dependent on the endoscopist and then endoscope imaging technology. Gaze analysis is an exciting and recent research tool to help further our understanding of luminal lesion detection by endoscopy.

Gaze analysis has become cheaper, less invasive, and thus more available as research tool. These trials show the valuable application of gaze analysis as a research tool in endoscopy. However, this full systematic review has only revealed a small number of trials and often these trials in themselves are small numbered as well and thus it appears this is a relatively new area of research.

Comparing lesion detection rates and expertise of endoscopists with gaze patterns has demonstrated potentially important signals towards better search strategies including focus on the left side of the lumen and general focus on the peripheries of the screen and lumen when performing diagnostic colonoscopy. This would potentially be useful in training of endoscopists as well as an objective measure of endoscopist expertise but the trials available so far are small in numbers and heterogeneous in methodology.

Similarly gaze analysis has shown a potential valuable application in training and the exciting work being conducted by Liu et al. may produce a trainerless training system which may help reduce the burden of training during a period where number of endoscopies required exceed the number of trained endoscopists available.

Novel endoscopic imaging technologies are rapidly being developed and will continue to appear. The ability to objectively assess the numerous technologies being promoted will be important to allow evidence-based incorporation of these systems into endoscopy practice and guidance.

Gaze analysis has been shown to be an excellent objective tool to compare these technologies to the current standard of white light endoscopy.

Gaze analysis in its early stages of application to endoscopic research but has demonstrated potential value in improving the quality of endoscopy through analysing the patterns of expert endoscopists, developing endoscopy training systems and as an objective tool to analyse endoscopic technologies.

3.AI in Endoscopy: A Meta-Analysis of Computer Aided Diagnostic Endoscopy (CADE) in Lesion Detection

Content from this Chapter was Published in (1):

Sivananthan A et al. Does computer-aided diagnostic endoscopy improve the detection of commonly missed polyps? A meta-analysis. *Clin Endosc.* 2022;55(3):355-364.
doi:10.5946/ce.2021.228

Content from this Chapter was Presented in (62):

Sivananthan A et al. Performance of Computer Aided Detection Systems in Flat, Sessile and Diminutive Adenomas: A Meta-analysis. Digestive Diseases Week 2021 (Virtual).

3.1 Background

Colonoscopy remains the gold standard diagnostic investigation and allows detection and resection of neoplastic lesions. National colonoscopy-based screening programmes have been proven to reduce the 10-year colorectal cancer risk (21,22). However, is it not possible to achieve 100 % mucosal visualisation with a standard colonoscope in a clean colon. This presents several limitations, including missed polyps. A meta-analysis including 15,000 tandem colonoscopies calculated a 26% adenoma miss rate.(63)

It has been shown that a 1% increase in adenoma detection rate (ADR) decreases cancer risk by 3% (20). Post-colonoscopy colorectal cancer (PCCRC) is a significant concern (64) estimated to be between 3.2% and 16.4% (65) with the majority of missed colorectal cancer bring attributable to a missed lesion during a prior colonoscopy(23). A recent meta-analysis showed significantly higher adenoma miss rates in proximal (defined as proximal to the splenic flexure) diminutive ($\leq 5\text{mm}$) and non-pedunculated adenomas (63) versus larger and pedunculated adenomas.

Advances in technology and healthcare in recent years have improved the ADR, including the introduction of high-definition endoscopes (66), strict quality performance indicators and adjuncts such as EndoCuff (Arc Medical Design). Progress in endoscopic therapeutic capabilities has also extended the type of lesions that are potentially resectable by endoscopic submucosal dissection(67).

More recently, CAdE (computer aided detection) systems in endoscopy which are based on convolutional neural networks (CNNs), have been validated and made commercially available. This novel technology has been shown to detect polyps in real-time with greater diagnostic accuracy than standard colonoscopy,(68) and lead to a higher ADR.

Previous studies have assessed the application of CAdE systems to endoscopic images and videos, retrospectively, in a research setting. More recently, there have been meta-analyses assessing the impact of CAdE systems on ADR in real-time (68–70). However, unlike other studies, this meta-analysis aims to provide an up-to-date analysis of the impact of real-time CAdE systems on the detection of the most commonly missed polyps, including proximal, non-pedunculated and diminutive lesions.

The aims of this chapter are:

1. To systematically review and analyse CAdE systems in real time lesion detection compared to standard colonoscopy.
2. To compare CAdE systems against standard WLE or HD endoscopy in detecting commonly missed colonic lesions (diminutive, proximal and sessile polyps).

3.2 Methodology:

This review was carried out and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.(71)

3.2.1 Search Strategy

A comprehensive literature search of published articles up until October 2020 was undertaken. Databases used include EMBASE, Medline and the Cochrane Library. Search terms used in EMBASE and Medline included “colon*”, “polyp”, “adenoma”, “artificial intelligence OR machine learning” and “computer aided or assisted and diagnosis* OR detect*”. Studies in the Cochrane Library were identified with the terms “colonic polyp”, “artificial intelligence” and “diagnosis, computer-assisted” (Appendix 2).

3.2.2 Outcomes

The primary outcomes for this study were mean adenoma per patient (MAP) and mean polyp per patient (MPP) for diminutive ($\leq 5\text{mm}$) and non-pedunculated (flat or sessile) lesions.

Mean lesions per patient were calculated rather than detection rates in this paper. This was due to the data available in the studies analysed. There is, however, good evidence that mean lesion per patient rates correlate with polyp detection rate (PDR) and ADR.(72,73)

3.2.3 Inclusion and Exclusion Criteria

Inclusion criteria were as follows:

- Randomised controlled studies (RCTs) reporting computer-aided detection of colorectal polyps during real-time colonoscopy.
- Studies reporting MPP, MAP; or studies with adequate information to calculate these data.
- Studies reporting the PDR or adenomas according to morphology, size and location.

- Studies reporting the ADR or PDR of computer-aided detection systems during real-time colonoscopy.
- Studies published or translated into English.

Exclusion criteria were as follows:

- Studies with no original data present (e.g. review article, letter).
- Studies with no full text available.
- Studies conducted in patients with inflammatory bowel disease (IBD).
- Studies greater than 20 years old.
- Studies without adequate data to calculate PDR and ADR, mean polyp per patient, or mean adenomas per patient, or not reporting these data.
- Studies with overlapping data to the largest and latest data set from centres publishing multiple studies.

3.2.4 Study Selection

Two authors (SN and AS) reviewed the articles. The retrieved articles were screened for duplicates: these were excluded. Titles and abstracts were then screened for relevance independently. Studies irrelevant to the research question were excluded. Remaining articles were reviewed in full and reference lists scrutinised for relevant studies.

Disputed articles were settled by consensus by a third party (NP) after screening and following full-text review. Inclusion and exclusion criteria were met by all included articles. The study screening and selection process is shown in Figure 3.1.

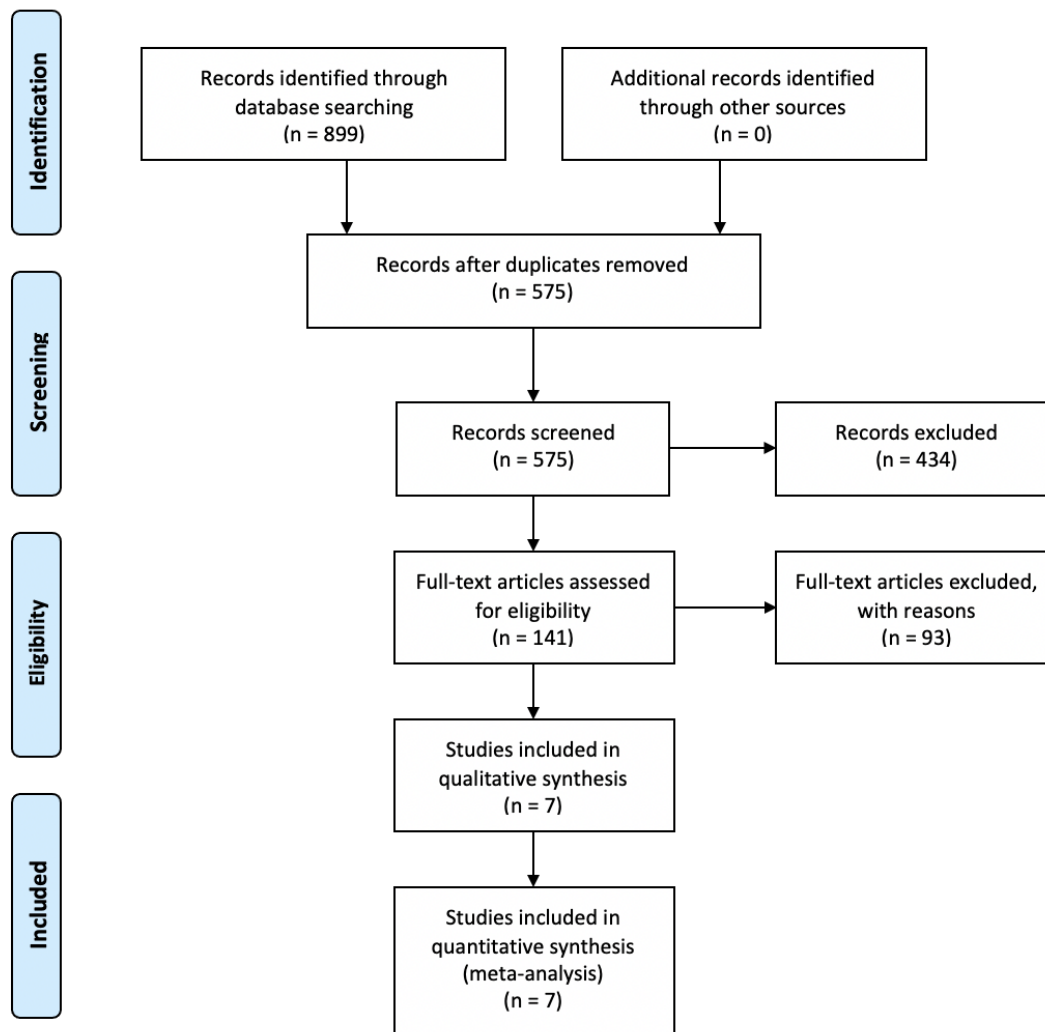


Figure 3.1 PRISMA (Preferred reporting items for systematic reviews and meta-analyses) flow diagram for study selection.

3.2.5 Data Extraction

Data were gathered from studies onto a standard spreadsheet template. For each study, we extracted the following data: study details (first author, year of publication, journal), study design (type of study, method of artificial intelligence [AI], exclusion criteria), and information regarding polyp characteristics (mean polyp per patient, mean adenoma per patient, morphology, size, location). Data was also gathered for the overall ADR and PDR in each study.

3.2.6 Study Quality Assessment

Study quality was independently assessed using the Jadad scale for RCTs (74). Studies with a Jadad score of 3 or more were considered “good” quality (Table 3.1).

Study	Randomisation (2)	Blinding (2)	An account of all patients (1)	Total / 5
Wang et al. 2019	2	1	1	4
Wang et al. 2020	2	2	1	5
Su et al. 2020	2	2	1	5
Gong et al. 2020	2	2	1	5
Liu et al. 2020	1	0	1	2
Luo et al. 2020	2	0	1	3
Repici et al. 2020	2	1	1	4

Table 3.1 Quality Assessment - Assessment of bias for RCTs using the Jadad scale; score ≥ 3 = good quality.

3.2.6 Statistical Analysis

Mean polyp and adenoma per patient by morphology and size were calculated by dividing the total lesions by number of patients for each group. Mean detection rates per patients are known to correlate well with polyp and adenoma detection rates (73).

Independent proportion and their differences were calculated and pooled through DerSimonian and Laird random-effects modelling. This considered both between-study and within-study variances which contributed to study weighting. Pooled values and 95% confidence intervals (CI) were computed and represented on forest plots. Statistical heterogeneity was determined by the I^2 statistic; where $<30\%$ was low, $30\text{--}60\%$ was moderate and $>60\%$ was high. Analyses were performed using Stata version 15 (StataCorp LP, College Station, Texas). Probability values ($p\text{-value}$) ≤ 0.05 were considered statistically significant.

3.3 Results

3.3.1 Eligible Studies

A total of 899 articles were identified from the database searches. After removing duplicates, 575 records were screened on the basis of titles and abstracts. A total of 141 articles were identified as appropriate for full-text review. Further evaluation, and application of the exclusion criteria, revealed seven studies which were included in this meta-analysis.

3.3.2 Study Characteristics

All seven studies deployed CAdE systems in real-time. Sufficient data was available from six studies for analysis of diminutive MPP, and from five studies for diminutive MAP. Four studies assessed MPP for non-pedunculated polyps and six studies reported MAP for non-pedunculated lesions. Six studies reported MPP and MAP for proximal (to the splenic flexure) lesions. One study did not report on adenoma detection, but analysed polyp detection only (75).

Sufficient data was provided in all studies to calculate MPP, MAP, mean diminutive polyps and adenomas per patient, mean proximal polyps and adenomas per patient and mean non-pedunculated polyps and adenomas per patient. Study characteristics are shown in Table 1. A total of 3052 polyps and 1847 adenomas were reported in 5028 patients with seven trials included with 4 different machine learning approaches and 4 different systems. A summary of the results can be found in Table 3.2.

Author and Year	Machine learning approach	No. of patients	No. of patients CAdE	No. of patients Control	Reported Polyps (total)	Reported Adenomas (total)	Withdrawal time (excl. biopsy) CAdE vs. control [mins]
Wang et al 2019 (76)	ANN-SegNet Architecture	1058	522	536	✓ (767)	✓ (424)	6.18 vs. 6.07 (p=0.15)
Wang et al 2020 (77)	ANN-SegNet						

	Architecture	962	484	478	✓ (809)	✓ (462)	6.48 vs. 6.37 (p=0.14)
Su et al 2020 (78)	DCNN	623	308	315	✓ (273)	✓ (169)	7.03 vs. 5.68 (p<0.001)
Gong et al 2020 (79)	DCNN	704	355	349	✓ (284)	✓ (85)	6.38 vs. 4.76 (p<0.0001)
Liu et al 2020 (80)	ANN	1026	508	518	✓ (734)	✓ (394)	6.82 vs 6.74 (p<0.001)
Luo et al 2020 (75)	CNN - YOLO	150	77	82	✓ (185)	X	6.22 vs 6.17 (p = 0.102)
Repici et al 2020 (81)	CNN - GENIUS	685	341	344	x	✓ (313)	6.95 vs 7.25 (p = 0.1)

Table 3.2 Study characteristics of included papers

ANN (artificial neural network), DCNN (deep convolutional neural network), CNN (convolutional neural network), YOLO (you only look once).

		CADe versus Control	Percentage Difference	Effect Size
Diminutive	MPP	0.69 vs 0.37	85.3 %	0.30 (95% CI 0.19 – 0.42)
	MAP	0.31 vs 0.17	80.0 %	0.13 (95% CI 0.09-0.18)
Non-pedunculated	MPP	0.84 vs 0.43	91.7 %	0.39 (95% CI 0.35-0.44)
	MAP	0.32 vs 0.19	71.5 %	0.05 (95% CI 0.02-0.07)

Table 3.3 Summary of CADe (computer-aided detection) versus control

Control vs MPP (mean polyp per patient) and MAP (mean adenoma per patient, diminutive and non-pedunculated), percentage difference and effect size.

3.3.3 Results- CADe versus Control

3.3.3.1 Diminutive lesions ($\leq 5\text{mm}$)

Six studies identified 1557 diminutive polyps in the CADe group (2254 patients) and 849 diminutive polyps in the control group (2278 patients) (Table 3.2). This equated to 0.691 diminutive polyps per patient in the CADe group versus 0.373 in the control group with a pooled effect size of 0.30 (95% CI 0.19 – 0.42) (Figure 3.2). This corresponds to an increase in detection rate of diminutive polyps with CADe of 85.3%.

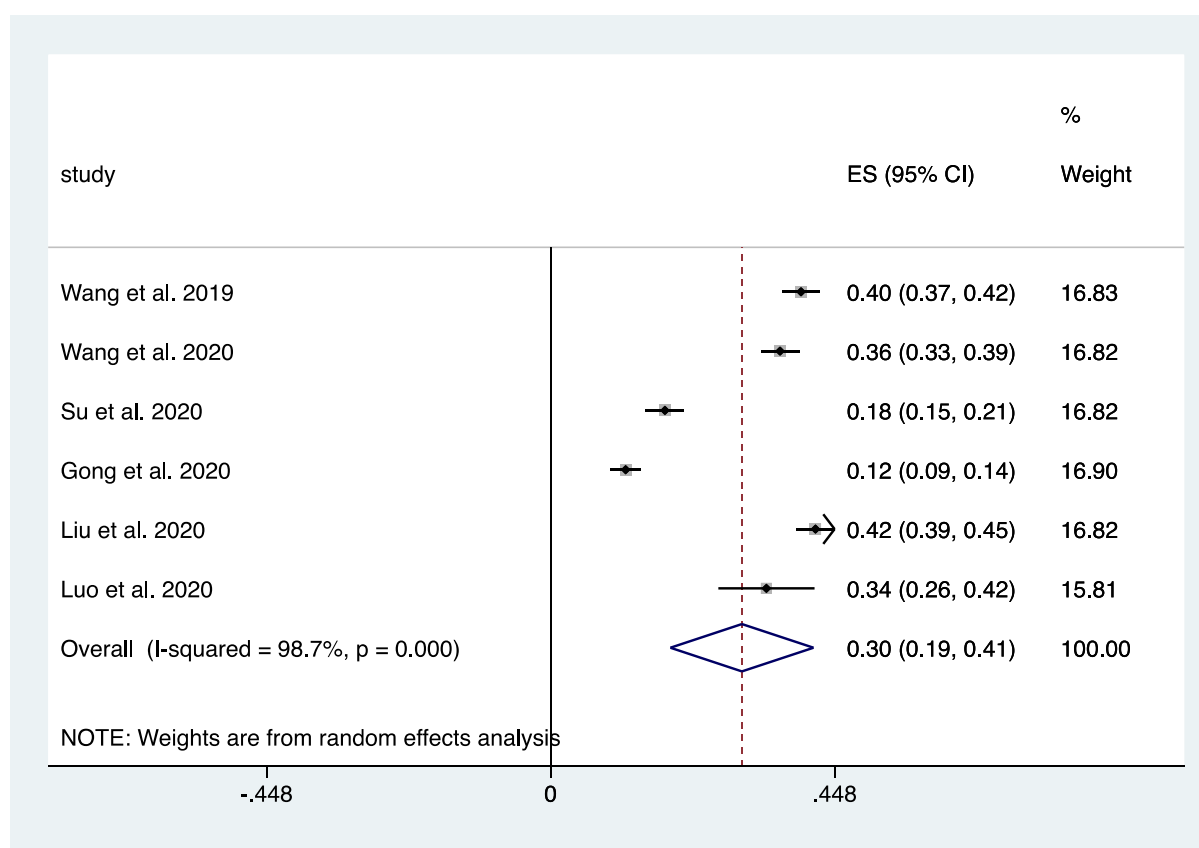


Figure 3.2 Pooled analysis of mean diminutive polyp per patient in CADe vs. conventional colonoscopy groups

Effect sizes (ES) are shown with 95 per cent confidence intervals. A random-effects model was used.

A total of five studies identified 680 diminutive adenomas in the CADe group consisting of 2177 patients and 381 diminutive adenomas in the control group with 2196 patients. There were 0.312 diminutive adenomas per patient in the CADe group and 0.173 in the conventional colonoscopy

group (Table 2), resulting in a pooled effect size of 0.13 (95% CI 0.09-0.18) Figure 3.3). The CADe group detected diminutive adenomas 80% more than conventional colonoscopy.

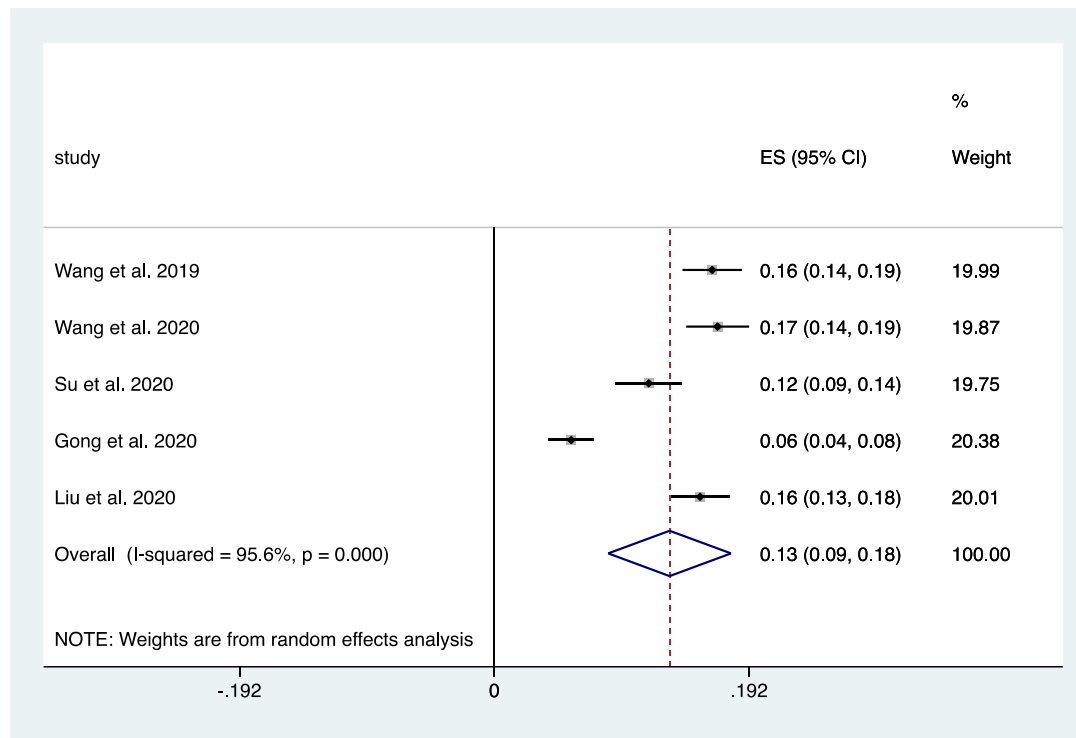


Figure 3.3 Pooled analysis of mean diminutive adenoma per patient in CADe vs. conventional colonoscopy groups.

3.3.3.2 Non-pedunculated lesions

A total of 1769 non-pedunculated lesions were identified in four studies, with 1158 in the CADe group (1337 patients) and 611 in the control group (1393 patients). This equated to 0.841 non-pedunculated polyps per patient in the CADe group and 0.439 non-pedunculated polyps in the conventional colonoscopy group (Table 2). An increase of 91.7% in detection of non-pedunculated polyps was shown with the use of CADe in the studies. A pooled effect size of 0.39 (95% CI 0.35-0.44) was generated when analysing non-pedunculated lesions in the CADe versus conventional group (Figure 3.4).

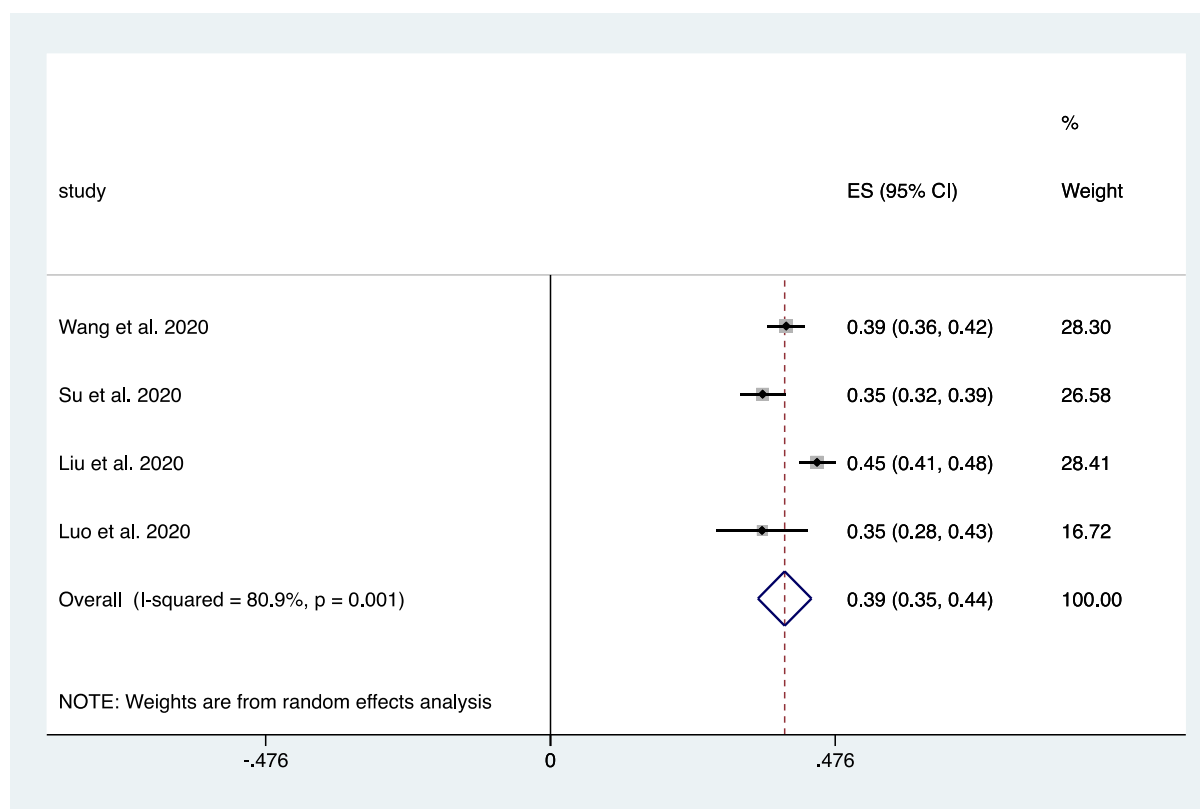


Figure 3.4 Pooled analysis of mean non-pedunculated polyp per patient in CADe vs. conventional colonoscopy groups

In six studies, 818 non-pedunculated adenomas were recorded in the CADe group (2518 patients) and 477 in the control group (2540 patients). This highlighted 0.325 non-pedunculated adenomas per patient in the CADe group versus 0.189 (Table 2) in the control group with a pooled effect size of 0.05 (95% CI 0.02-0.07; figure 3). The CADe system detected non-pedunculated adenomas with an increased rate of 71.5% when compared to conventional colonoscopy (Figure 3.5).

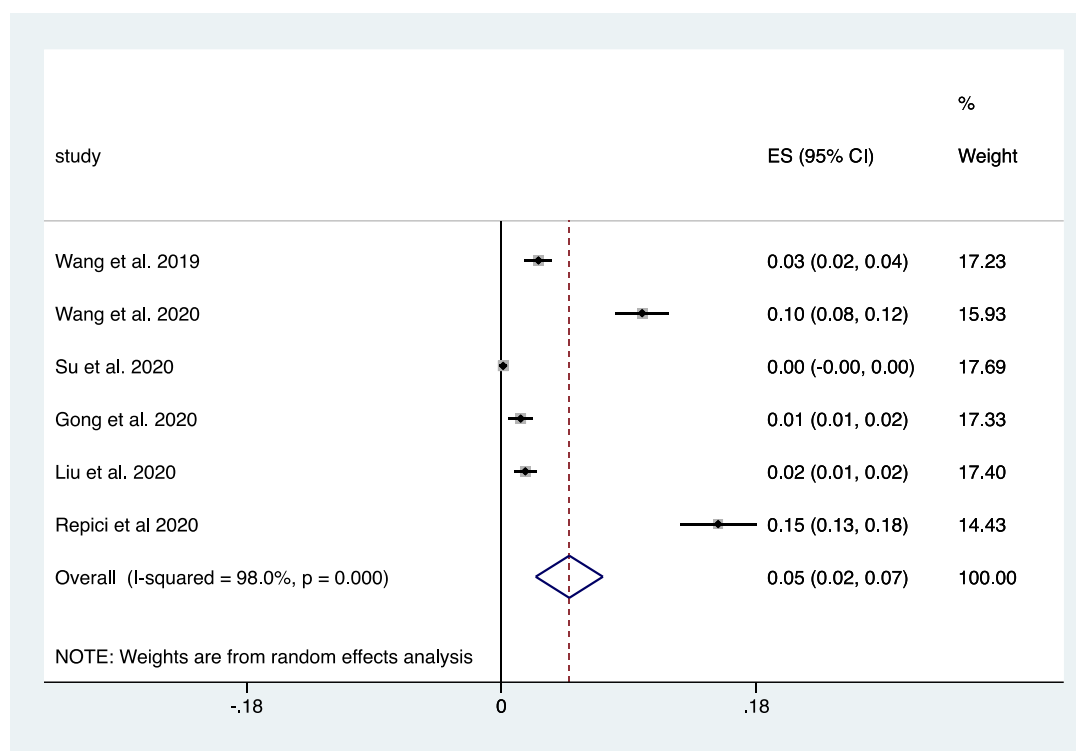


Figure 3.5 Pooled analysis of mean non-pedunculated adenoma per patient in CADe vs. conventional colonoscopy groups

3.3.3.3 Proximal lesions

A total of 4523 proximal lesions were identified in seven studies, with 837 in the CADe group (2254 patients) and 448 in the control group (2278 patients). This equated to 0.371 proximal polyps per patient in the CADe group and 0.197 proximal polyps in the conventional colonoscopy group (Table 2). An increase of 88.9 % in detection of proximal polyps was shown with the use of CADe in the studies. A pooled effect size of 0.17 (95% CI 0.09-0.24) was generated when analysing non-pedunculated lesions in the CADe versus conventional group (Figure 3.6).

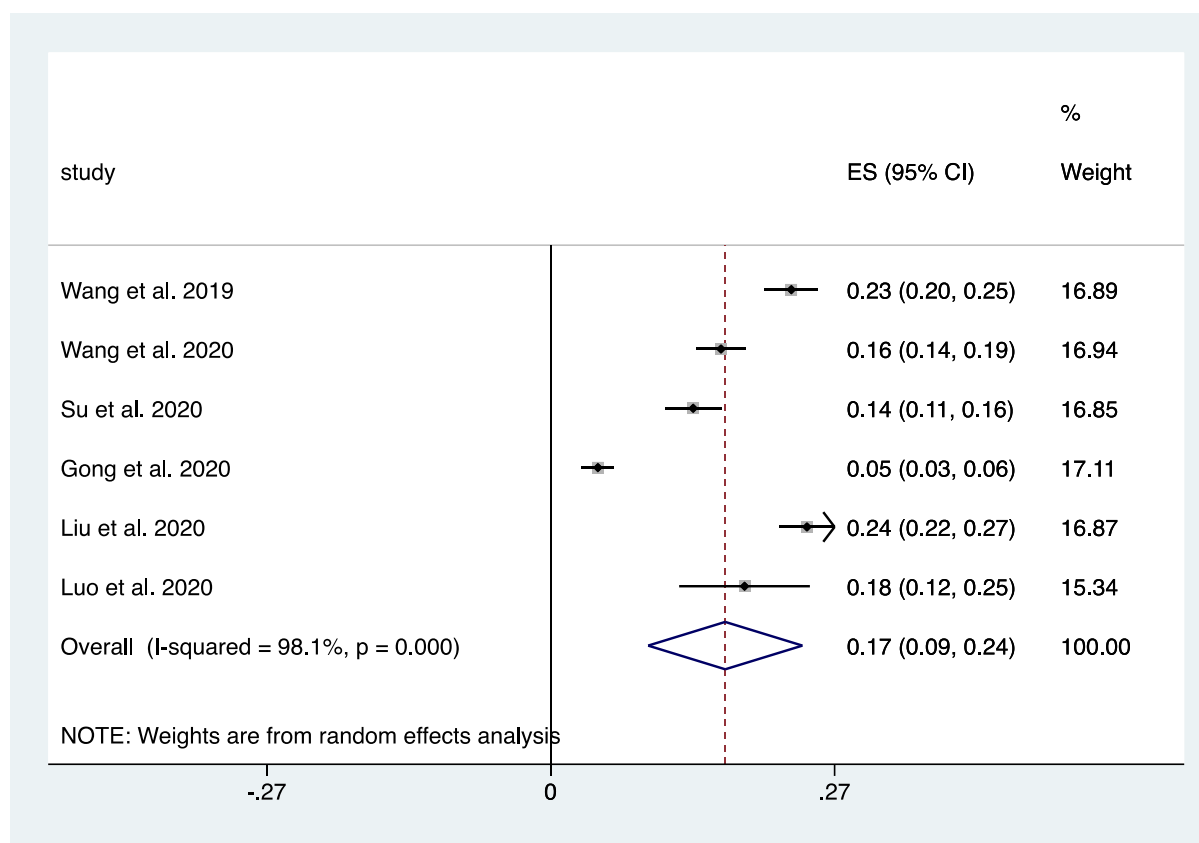


Figure 3.6 Pooled analysis of mean proximal polyps per patient in CADe vs. conventional colonoscopy groups.

In seven studies, 659 proximal adenomas were recorded in the CADe group (2518 patients) and 423 in the control group (2540 patients). This highlighted 0.262 proximal adenomas per patient in the CADe group versus 0.167 in the control group (Table 2) with a pooled effect size of 0.09 (95% CI 0.07-0.12; figure 3.8). The CADe system detected proximal adenomas with an increased rate of 57.2% when compared to conventional colonoscopy.

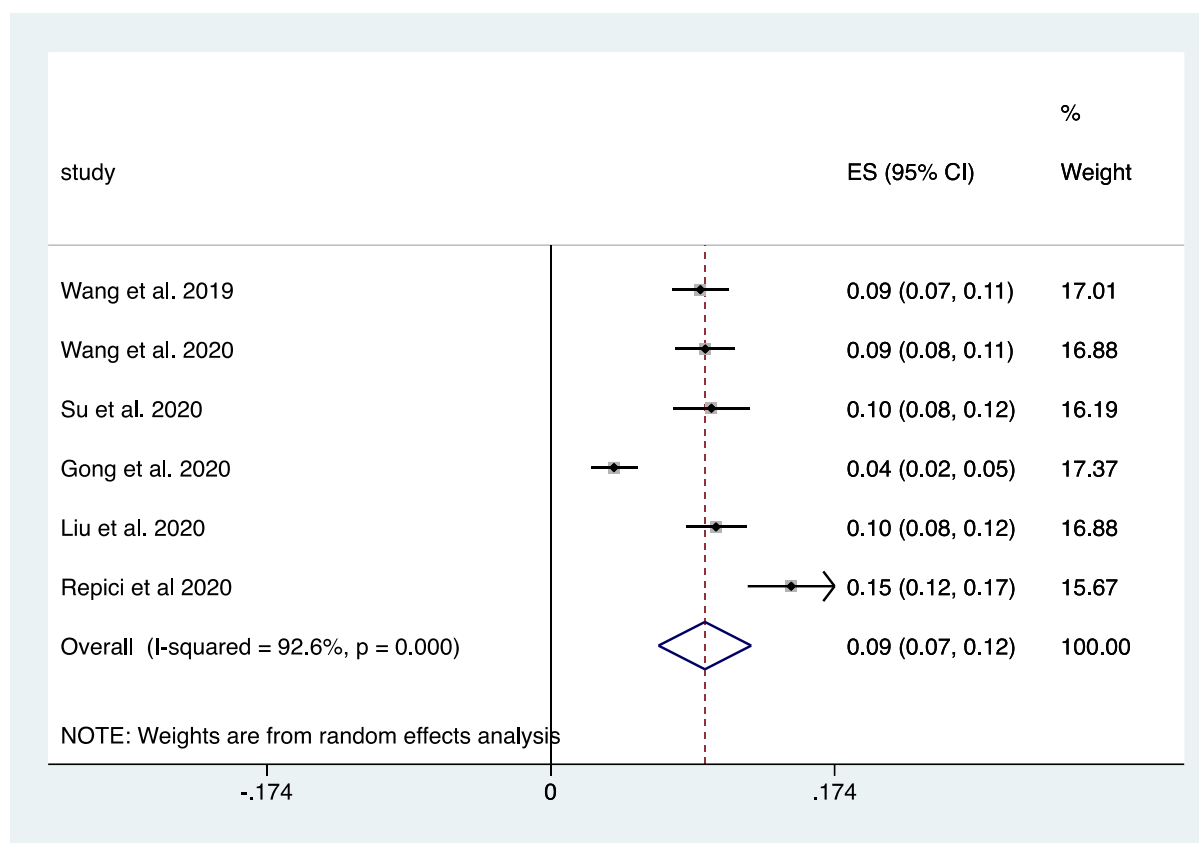


Figure 3.7 Pooled analysis of mean proximal adenomas per patient in CADe vs. conventional colonoscopy groups.

3.3.4 ADR and PDR

Overall, six studies assessed the ADR for CADe systems compared to standard colonoscopy, and six studies assessed the PDR in the same way (Table 3.4). All studies showed an improvement in ADR and PDR with the use of CADe systems when detecting polyps in real-time. The average ADR for CADe versus standard colonoscopy was 33.65% and 22.85%, respectively, with a range of 16%-54.8% for CADe and 8%-40.4% for standard colonoscopy.

Authors & Year	PDR – CAdE [%]	PDR – control [%]	ADR – CAdE [%]	ADR – control [%]
Wang et al 2019 (76)	45.02	29.1	29.12	20.34
Wang et al 2020 (77)	52	37	34	28
Su et al 2020 (78)	38.31	25.4	28.9	16.5
Gong et al 2020 (79)	47	34	16	8
Liu et al 2020 (80)	43.65	27.81	39.1	23.89
Luo et al 2020 (75)	38.7	34	N/K	N/K
Repici et al 2020 (81)	N/K	N/K	54.8	40.4

Table 3.4 Summary of CAdE (computer-aided detection versus control for polyp and adenoma detection).

(N/K – not known)

3.3.5 Heterogeneity of Studies

There was a high degree of variation between studies. The heterogeneity was statistically significant when comparing the studies ($p < 0.05$). The variation amongst studies ranged between 95.6% and 98.7%.

3.3.6 Quality Assessment

The assessment of bias for the studies using the Jadad scale is shown in Appendix 3. Most of the RCTs scored 3 or more on the Jadad scale and were therefore considered to be of good quality, except for one study which scored 2 suggesting poor quality.

3.4 Discussion

This meta-analysis assesses the real-time performance of CADe systems to detect lesions most commonly missed by endoscopists and builds on existing data that these systems improve the ADR and PDR overall. The results in this review demonstrate that CADe systems performed better than standard colonoscopy in detecting diminutive and non-pedunculated polyps, including adenomas. The CADe systems demonstrated a percentage increase in detection of between 57% and 92%. The effect size was more pronounced in polyp detection versus adenoma detection.

The difference in withdrawal times observed in most of the RCTs was not significant when using the CADe systems. This suggests that the endoscopy workflow will not be substantially affected by the addition of a CADe system, nor will it take longer to detect “tricky” lesions during the procedure. However, three studies did show a significantly higher withdrawal time for CADe systems (78–80), and so it is difficult to gauge the realistic impact that CADe systems have on withdrawal time given the variability in type of systems used and relative infancy of such CADe systems in a real-time healthcare setting.

It is known that increasing adenoma detection reduces colorectal cancer risk. It is also recognised that missed lesions cause the majority of PCCRCs (23). It is, therefore, reasonable to assume that the significant increase in detection in the most commonly missed adenomas would translate into reduced PCCRC rates.

An increase in polyp detection will often also include benign lesions such as hyperplastic polyps. In order to improve the ADR, AI-based technology aimed at characterisation of polyps during endoscopy is being optimised. Once effective, this technology will allow a strategy of “resect and discard” or “diagnose and leave” for small polyps, which has so far defied large-scale attempts at introduction into everyday practice (82,83).

The papers included in this meta-analysis used CADe systems based on neural networks, however, the type of architecture and algorithm in each study differed which likely contributed to the large heterogeneity in the studies. Although our findings may highlight the overall impact

of CAdE systems in detecting this subset of lesions, it may dilute and therefore underestimate the effect of individual systems. Endoscopic experience and withdrawal time was similarly not standardised across studies which may contribute to the heterogeneity of this meta-analysis.

Previous meta-analyses have excluded the paper by Gong et al. as the system used in the study focussed on quality of withdrawal rather than direct lesion detection (79). Our meta-analysis focuses on the general application of CAdE systems and its impact on lesion detection, and therefore, we included this paper in our analysis. This likely also contributed to the large heterogeneity. More real-time studies will allow focussed analyses on different CAdE systems and their applications.

The level of experience of the endoscopists participating in the studies varied from 1-3 years of experience(79) to 4-6 years (78), with different overall procedure numbers. Previous studies have demonstrated a significant correlation between number of years' endoscopy experience and the ADR (84). Endoscopists with a higher degree of skill and performance are more likely to detect diminutive or non-pedunculated polyps. It would be important to assess if impact of CAdE systems correlates with level of experience to allow it to be deployed in a cost-effective way.

The malignant potential of diminutive adenomas is unclear. Vleugels et al. report a low risk of diminutive lesions containing advanced pathology (5.6%) and cancer (0.07%) (85). Kim et al. however showed an increased risk of metachronous cancer in the presence of three or more non-advanced diminutive adenomas and advanced pathology (86). The number of diminutive lesions does play a role in some screening programmes internationally. Optical diagnosis using an AI-based system may improve overall detection of colonic pathology and may lead to a resect and discard pathology with respect to diminutive lesions.

3.5 Conclusion

A key role of luminal endoscopy is detection of lesions and an increase in lesion detection has a well-documented tangible reduction in cancer and it is for this reason screening programmes are now delivered in most developed countries.

This study demonstrates the ability of CADe to improve detection of the most commonly missed colonic polyps and thus a likely reduction in PCCRC. However, the evidence base for real-time CADe in endoscopy is still relatively small and further trials are required, including comparison of different systems and different levels of experience, before this is incorporated more widely into standard clinical practice. Nonetheless the available data strongly points to the potential significant added value of CADe system in endoscopy.

4. Orientation in Endoscopy: A Cross Sectional Descriptive Survey of Endoscopists Orientation During Endoscopy

Content from this Chapter was Published in (87):

Sivananthan A et al. Orientation in upper gastrointestinal endoscopy - the only way is up. World J Gastrointest Endosc. 2023 Mar 16;15(3):146-152. doi: 10.4253/wjge.v15.i3.146.

4.1 Background:

Accurate orientation by the endoscopist plays a critical role in the detection and management of luminal lesions alongside the technical imaging capabilities of the endoscope. Improving imaging capability of the endoscope provides a more accurate image to endoscopists but the endoscopist is still required themselves to accurately orient themselves based on the image they see. Appropriate localisation and orientation within the lumen are important to risk stratify lesions accurately and allow appropriate management of the lesion.

This chapter aims to:

1. Outline the role of orientation in Endoscopy
2. Determine the ability of endoscopists to orient and localise themselves in the UGI tract

4.1.1 Orientation in Endoscopy

Orientation in LGI Endoscopy

Accurate orientation in LGI endoscopy provides important information to help guide management. Certain distributions of colonic inflammation may guide endoscopists towards an ischaemic cause over infection which will significantly change management. Localising cancerous lesions accurately helps guide the extent of surgical resection. The right colon has a

thinner wall and requires lower electrocautery settings than the left side. Inappropriate use of left sided colonic electrocautery on the right side increases the risk of perforation, thermal injuries and early and late colonic bleeding.

The colon is a mobile structure and mesenteric attachment allows stretch and 'looping' of the colon. Pushing a colonoscope into the patient may provide no luminal progress but instead stretch the colonic mesentery causing looping, patient discomfort and increased perforation risk.

Orientation in LGI endoscopy has been improved significantly by scope guidance technologies such as ScopeGuide (Olympus, Tokyo) and Scope SCOPEPILOT (Pentax, Tokyo) (Figure 4.1) (88). Magnetic coils housed in the colonoscope itself allow an accurate 3D reconstruction of the endoscope configuration to be displayed to the endoscopist in real time. This allows accurate orientation and location of the tip within the colon and identification of colonic looping allowing resolution of the loop.



Figure 4.1 SCOPEPILOT (Pentax, Tokyo)

4.1.2 Orientation in UGI Endoscopy

Oesophagogastroduodenoscopy (OGD) is the gold standard investigation for UGI tract allowing direct visualisation, tissue sampling and a widening remit of therapeutic curative procedures for early cancers.

Orientation within the UGI tract during endoscopy is challenging due to the complex interaction between the flexibility of the scope, the multiple degrees of freedom of the endoscope tip, use of torque and the predominant focus on the (inverted) displayed image.

Endoscopy's role in diagnosing UGI cancer continues to advance, with a better understanding of precursor changes such as Barrett's and atrophic gastropathy and evolving technologies like image enhanced endoscopy and computer aided detection systems. Despite this 11.3% of UGI cancers are missed by OGD (89). The role of endoscopy in the management of benign UGI conditions has also improved. There are increasing therapeutic options to intervene endoscopically on complex bleeds, or UGI perforations, with patients who historically would have required surgery now often being managed endoscopically.

There are growing numbers of guidelines and statements to help support approaches to surveillance and management of UGI pathology including a standardised approach to photo-documentation of the UGI tract (90–92). There are numerous widely accepted protocols on UGI surveillance such as the Seattle protocol (14) for assessing Barrett's and the Sydney protocol for assessing chronic gastritis. These guidelines require accurate identification of the endoscopic anatomy for appropriate sampling and photo- documentation.

For example, chronic atrophic gastritis is a well-recognised precursor lesion to gastric cancer but the risk is significantly correlated to its anatomic distribution which is assessed on endoscopy and dependent on the endoscopist's accurate orientation within the UGI tract. If CAG is suspected the Sydney protocol of biopsies is undertaken. The Sydney protocol requires separate biopsies of the gastric antrum, incisura, lesser curve and greater curve (Figure 4.2) (14).

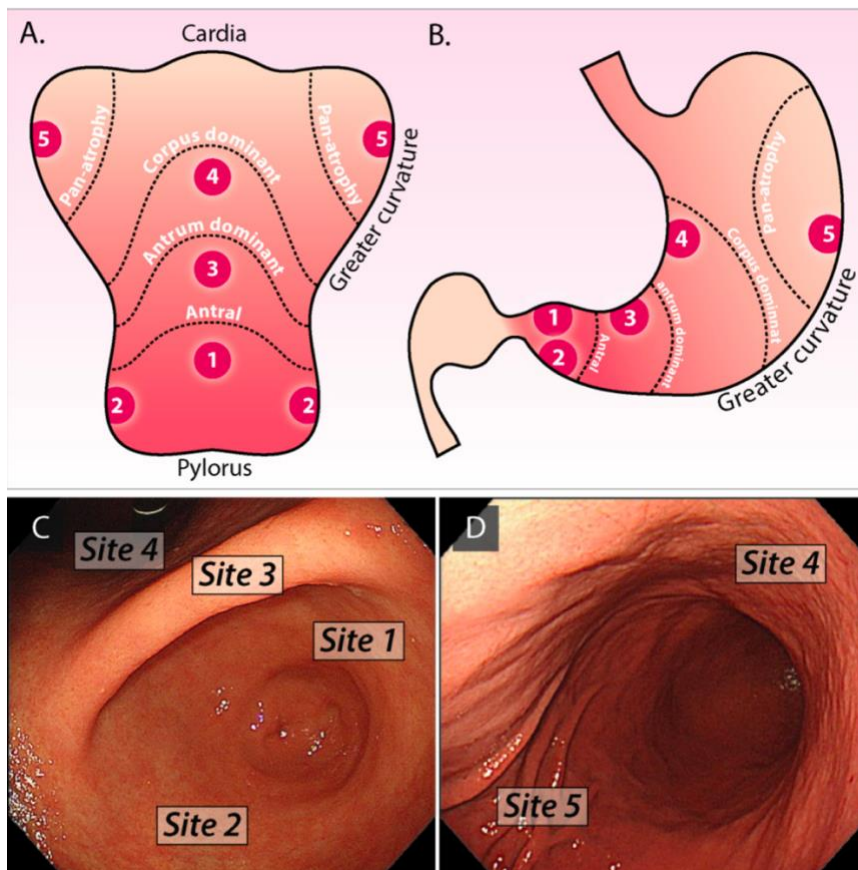


Figure 4.2 Sydney Protocol Biopsy Targets

This requires appropriate orientation and localisation endoscopically within the stomach differentiating between the greater curve and lesser curve, and the corpus and antrum. Appropriate localisation and of GIM for example are key (93). When comparing the Magenstrasse pattern (lesser curve from cardia to pylorus and greater curve pyloric antrum) and the diffuse pattern (entire gastric mucosa other than fundic areas) to focal (foci in lesser curve and incisura) and antrum predominant (antral) GIM, Magenstrasse had a 5.7-fold increased gastric adenocarcinoma risk with diffuse pattern GIM having a 12.2 fold increase.

The reported location of UGI pathologies such as ulcers directly impacts post-endoscopy investigation and management. Gastric ulcers located on the greater curve are more commonly malignant, whereas benign gastric ulcers occur predominantly on the lesser curve⁶. Ulceration in the first part of the duodenum (D1) is more likely to lead to perforation if the ulcer is located on the anterior wall and although the overall perforation rate in peptic ulcer disease is relatively low most ulcers that do perforate are anterior D1 (94)

The gastroduodenal artery is located directly behind the posterior aspect of the duodenum. Ulcers on the posterior duodenal wall are at risk of eroding into this artery which can result in massive bleeding and as such carry a worse prognosis (95). Posterior duodenal ulcers are also associated with a higher re-bleeding risk (96,97) and the accurate identification of a posterior duodenal ulcer is important to understand the proximity of the gastroduodenal artery and thus the understanding of endoscopic limits and appropriate targets for interventional radiology or surgery if required.

The PubMed, Cochrane Library and Embase databases were searched until January 10th 2023 to identify relevant research articles. This revealed limited available data on orientation within the UGI tract. One paper was identified from 1992 showing only a 28% accuracy in endoscopists identifying the posterior duodenal bulb (98).

The aim of this study is to evaluate endoscopists' visual spatial orientation within the UGI tract.

4.2 Methodology

4.2.1 Study Design

A cross-sectional descriptive survey study design was used. The study was approved by the Imperial College London institutional review board. A questionnaire was developed by the authors using anonymised endoscopy pictures taken by AS (with consent for publication given by the patients).

Anonymised endoscopic pictures of the gastro-oesophageal junction (GOJ), gastric body and the first two parts of the duodenum were used. Images were annotated in each of the four quadrants of the image (Figures 4.3, 4.4, 4.5, 4.6) to give four options. The patient position (left lateral decubitus) was specified. Orientation of the quadrants in the images and corresponding correct responses were determined in a two-stage process, initially proposed by AS/GK and agreed by NP/KP in the context of the available literature (14,91,92,99–102). The questionnaire was developed in Qualtrics™. Demographics including specialty and endoscopic experience were also collected.

The primary outcome was the percentage of correct answers amongst all surveyed. Secondary outcomes were the percentage of correct answers from experienced versus novice endoscopists.

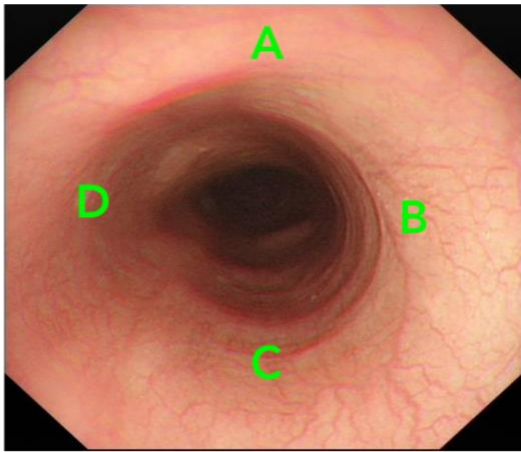


Figure 4.3 Image of mid oesophagus with anterior oesophagus corresponding to “D”

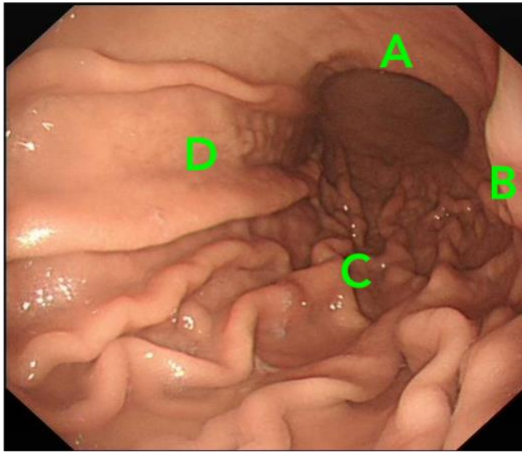


Figure 4.4 Image of mid gastric body with anterior stomach corresponding to “D”

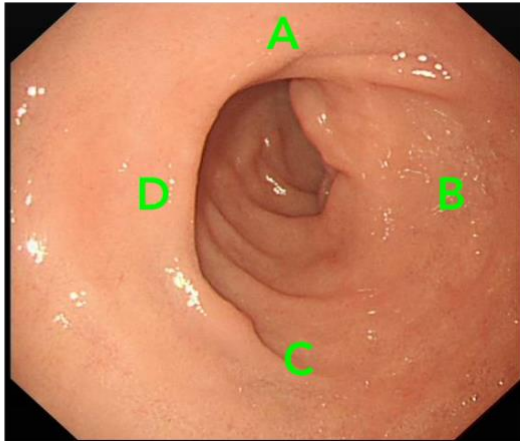


Figure 4.5 Image of the first part of the duodenum with the anterior duodenum corresponding to “D”

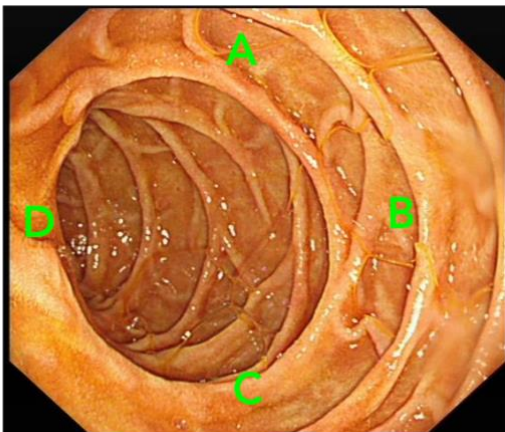


Figure 4.6 Image of the second part of the duodenum with the posterior duodenum corresponding to “C”

4.2.2 Data Collection

The survey was distributed through existing national endoscopic research networks including the ‘digital gastroenterology training network’ and opportunistically to endoscopists at the British Society of Gastroenterology Annual Meeting. Inclusion criteria was any experience performing OGDs in adult patients. There were no exclusion criteria. Clinical role of the endoscopists were asked including consultant (equivalent to attendee), registrar (gastroenterology specialist trainee), senior house officer (early-stage medical training) and clinical endoscopists (specialist nurses trained to independently perform endoscopy).

4.2.3 Statistical Analysis

Results were collected anonymously using the Qualtrics software and exported to Microsoft Excel for basic statistical analysis. Experienced endoscopists were classified as those who had performed more than 1000 OGDs. Novice endoscopist were classified as those who has completed 1000 or less OGDs. Percentages were used to analyse the discrete data for all subjects. Pearson's Chi-squared test was applied to compare the two groups using a p value below 5% to denote significance.

4.3 Results

4.3.1 Demographics

There were 188 respondents to the survey (Table 4.1). Of these: 74 respondents were consultants, 91 were registrars and 23 were nurse endoscopists. Most were physicians (184) and four were surgeons. There were 163 independent accredited endoscopists and 25 training endoscopists. There were 86 experienced endoscopists having completed more than 1000 endoscopies with 102 novice endoscopists completing 1000 or fewer endoscopies.

Grade	
	Percentage (Number)
Consultant	39.4% (74)
Registrar	48.4% (91)
Nurse Endoscopist	12.2% (23)
Speciality	
Medicine	97.9% (184)
Surgery	21.% (4)
Accreditation	
Independent	86.7% (163)
Not Independent	13.3% (25)
Experience	
Experienced (>1000)	45.7% (86)
Novice (≤1000)	54.3% (102)

Table 4.1 Demographics of survey respondents

4.3.2 All Respondents

44.4% of all respondents identified the anterior oesophagus correctly (Table 4.2). 48.4% of all respondents were able to identify the anterior stomach correctly. 43.1% of all respondents were

able to identify the anterior of the first part of the duodenum correctly. 47.3% correctly identified the posterior of the second part of the duodenum.

All (188)	
Anterior Oesophagus	32.4% (61)
Anterior Stomach	48.4% (91)
Anterior D1	43.1% (81)
Posterior D2	47.3% (89)

Table 4.2 Correct responses by total respondents – percentage and absolute number.

4.3.3 Experienced versus Novice

Experienced endoscopists were significantly more likely than novice endoscopists to identify the anterior oesophagus (44.2% vs 22.5%, X^2 (1, N = 188) = 9.97, p = .002), the anterior stomach than novice endoscopists (61.6% vs 31.3%, X^2 (1, N = 188) = 11.10, p = .001) and the first part of the duodenum than novice endoscopists (51.2% vs 36.3%, X^2 (1, N = 188) = 4.22, p = .040) (Table 4.3).

There was no significant difference between experienced endoscopists and novice endoscopists in identifying the posterior of the second part of the duodenum (41.9% vs 52.0%, X^2 (1, N = 188) = 1.91, p = .167).

	Experienced (86)	Novice (102)	P value
Anterior Oesophagus	44.2% (38)	22.5% (23)	.002
Anterior Stomach	61.6% (53)	31.3% (38)	.001
Anterior D1	51.2% (44)	36.3% (37)	.040
Posterior D2	41.9% (36)	52% (53)	.167

Table 4.3 Correct responses: expert endoscopists versus novice endoscopists – percentage and absolute number.

4.4 Discussion

This study demonstrates that the majority of endoscopists surveyed were unable to accurately identify key landmarks within the UGI tract. This is in keeping with previous work showing the majority of endoscopists being unable to identify the posterior duodenal bulb in 1992. Although there is no clear evidence that accuracy of orientation and landmark identification during endoscopy has a direct impact on patient outcomes there are logical reasons to think that this would be the case.

Consensus statements on photo-documentation, including those from the British Society of Gastroenterology (BSG), European Society of Gastrointestinal Endoscopy (ESGE), American Gastroenterological Association (AGA), American Society of Gastrointestinal Endoscopy (ASGE) and the World Congress of Gastroenterology (WCOG) (90,102) are reliant on endoscopists correctly identifying key UGI landmarks. Based on our findings there is doubt that many respondents are accurately recognising the position of anatomical landmarks and pathology which may have an impact on accurate photo-documenting and thus by inference inspecting all the anatomical areas suggested. Accurate orientation and localisation are important for risk stratification. Based on these results it is unclear if endoscopists are equipped to accurately grade distribution of chronic atrophic gastritis for example or appropriately take histological samples as per the Seattle protocol as this required differentiation of the greater and lesser curve for example.

Accurate anatomical identification of duodenal ulcer location may allow appropriate planning for further management and risk stratification but only a minority of respondents were able to differentiate the anterior and posterior duodenum. Gastrostomy feeding tubes placed endoscopically are accessed via the anterior stomach but the majority of endoscopists were also unable to accurately identify this.

With the increasing role of the multi-disciplinary team (MDT), reports are commonly interpreted by non-endoscopists, and accurate reporting of lesion location would presumably advantage other specialists when considering management or correlating with radiological findings.

Although there is now wider availability of access to photo-documentation from previous endoscopies, the accurate reporting of the location of lesions may also offer medicolegal support in providing clear evidence that a lesion is new. This is especially relevant in the context of the high reported rate of UGI cancers missed at endoscopy.

Experienced endoscopists were significantly more likely to respond correctly in all but the question related to the second part of the duodenum. This suggests that experienced endoscopists more reliably orientate themselves correctly within the UGI tract and posits that understanding of orientation is gained experientially. Although, the correct recognition of posterior D2 by experienced versus novice endoscopists was not statistically significant, which suggests that experience is not the only factor impacting accurate endoscopic orientation.

The focus on the inverted on-screen image may lead to discrepancies in reported locations, often reports are written with lesions documented with respect to their position on a clock face. However, this does not always correlate with the anatomical orientation. For example, left of the screen, when looking at the gastro-oesophageal junction, does not necessarily correlate to the anatomical left of the patient as the orientation of the screen is dependent on both patient position and steering of the endoscope. Orientation based on landmarks provides an objective assessment of location. The inaccuracy of the responses may be due to selecting the responses corresponding to the location on the image itself (i.e. left of the image) rather than based on the anatomical landmarks.

There were limitations to this study including the use of still images which is not akin to real time endoscopic views which may improve orientation. The sample was of British endoscopists and is therefore not generalisable to other countries with different approaches to training and certification.

4.5 Conclusion

This study has signalled that orientation within the upper GI tract by endoscopists is inaccurate. Endoscopic orientation does appear to improve with experience. Accurate orientation may have beneficial impact on patient outcomes with respect to interventional procedures including rescoping after an UGI bleed and informed arterial embolisation. Similarly appropriate lesion localisation allows appropriate risk stratification of UGI lesions such chronic atrophic gastritis. Accurate orientation of the CAG allows appropriate careful surveillance to prevent and identify transformation to gastric cancer and prevent inappropriate surveillance in limited CAG which has a very low transformation risk. Further work is required to research the cause of this disorientation. With advanced endoscopic technology there is the potential for novel solutions to assist endoscopic orientation during this high cognitive workload procedure.

5. Therapeutic Endoscopy: The Interventional Endoscopist' Toolbox

Content from this Chapter was Published in (66,67):

Sivananthan A et al. The evolution of lower gastrointestinal endoscopy: where are we now?. *Ther Adv Gastrointest Endosc.* 2020;13:2631774520979591. Published 2020 Dec 20. doi:10.1177/2631774520979591

Sivananthan A et al. Endoscopic submucosal dissection: an update on tools and accessories. *Ther Adv Gastrointest Endosc.* 2020;13:2631774520957220. Published 2020 Sep 28. doi:10.1177/2631774520957220

5.1 Background

Luminal endoscopy has evolved from a diagnostic adjunct to a complex subspecialty, in its own right, with an evolving therapeutic role. Endoscopy plays a major role in the prevention, diagnosis and increasingly the management of gastrointestinal cancer.

As described in the preceding chapters, endoscopy plays an important role in detection of precancerous and cancerous lesions, CAdE can improve this detection. The role of endoscopy in removing these detected lesions is similarly evolving. In the UGI tract, early identification of advanced Barrett's or chronic atrophic gastritis allows early treatment and management including radiofrequency ablation, mucosal and submucosal resection. In the LGI tract, adenomas are the predominant precursor lesion and identification and removal of these is a key function of endoscopy in preventing colorectal cancer (19). The introduction of screening programmes plays an important role in mitigating this risk with case control studies in Germany and the USA suggesting such programmes reduce 10 year colorectal cancer risk (21,22). More advanced lesions that previously would have required surgery can now be removed endoscopically allowing organ preservation through more advanced therapeutic endoscopic procedures.

In this chapter the main forms of polypectomy are presented from simple biopsy to endoscopic submucosal dissection followed by a detail look at the tools available to ESD practitioners.

The aims of this chapter are to:

1. Outline the role of endoscopy in therapeutic resection
2. Review the available endoscopic instruments to therapeutic instruments

5.2 Therapeutic Luminal Endoscopy

Successful polypectomy aims to remove a luminal polyp entirely with no residual disease and to minimise disease recurrence and polypectomy related complications such as bleeding or perforation. There are multiple techniques to approach polypectomy dependent on size, morphology, location and endoscopist experience.

5.2.1 Biopsy Forceps Polypectomy

Biopsy forceps are used by placing and closing the jaws of the instrument around the target tissue and physical avulsion of the sample. There are a wide variety of forceps available (Figure 5.1) (103) including serrated and non-serrated jaws, forceps with a central stabilising needle and jumbo-sized forceps (104–106). Hot biopsy forceps allow coagulation currents to be deployed simultaneously to avulsion but have mainly fallen out of favour (107–110). Cold snare polypectomy is increasing favoured in any diminutive polyps above 3mm with improved complete resection rates versus biopsy forceps polypectomy (111,112).

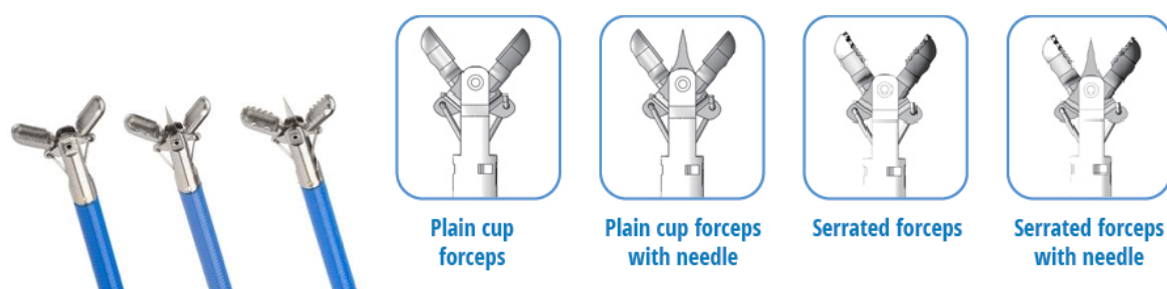


Figure 5.1 STERIS (Mentor, Ohio, USA) range of forceps.

5.2.2 Snare Polypectomy

Snare polypectomy involves placement of a loop of braided monofilament around the target tissue and closure around this with subsequent avulsion. Cold snare polypectomy uses mechanical force alone for polypectomy (Figure 5.2) (113). Addition of a monopolar electrode allows hot snare polypectomy through the use of electrosurgical cutting and coagulation currents.

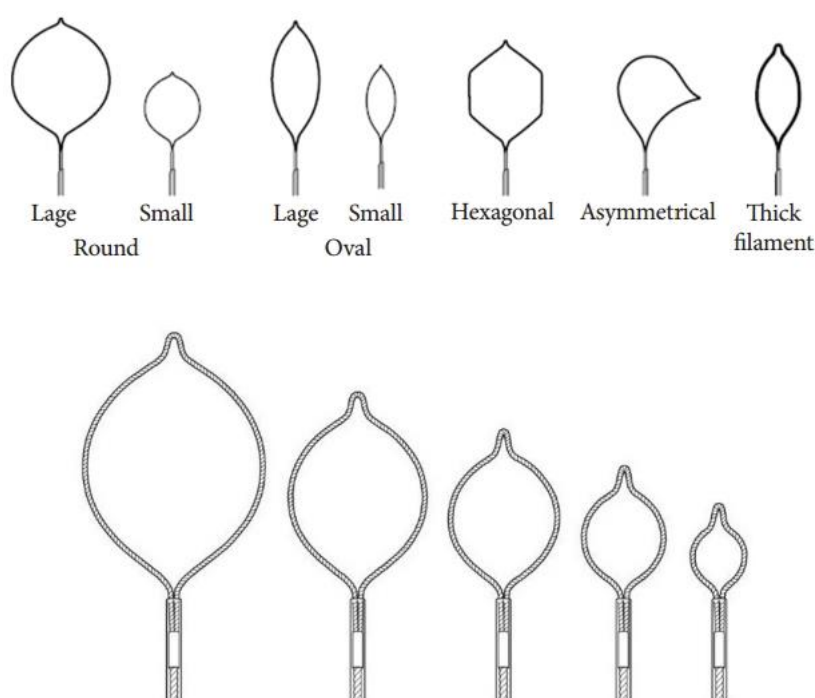


Figure 5.2 Range of endoscopic snares

Cold snare polypectomy has increasingly become the mainstay resection procedure of diminutive polyps. Multiple studies have compared cold to hot snare polypectomy in smaller polyps with no difference in complete resection rates (114,115) with a trend towards lower rate of post polypectomy bleeding in cold snare polypectomy (116,117) and in those on anticoagulant therapy (118–120). This is likely due to an increase in defect size seen one day after hot snare polypectomy and a higher percentage of submucosal tissue capture (121,122).

5.2.3 Endoscopic Mucosal Resection

Endoscopic mucosal resection (EMR) is a technique used to remove larger sessile or flat lesions not amenable to standard polypectomy. The main intent of EMR is to increase the separation between the mucosa and muscularis propria to allow safer resection of superficial lesions (123). EMR may involve resection of the entire lesion as one piece referred to as en-bloc or in multiple resections referred to as piecemeal.

The three main techniques used in EMR are conventional hot EMR, cold EMR and underwater EMR (Figure 5.3) (124).

Hot, or conventional EMR involves submucosal injection below the lesion and resection of the lesion via a hot snare (125).

Cold EMR similarly utilises submucosal injection, but subsequent snaring is done without electrocautery. Emerging evidence suggests this may be safer than conventional EMR with a reduced rate of bleeding, perforation and post-polypectomy syndrome and movement in (126). There is an increasing movement toward cold EMR in this 'cold revolution' (127).

Underwater EMR used fluid insufflation of the lumen to float the lesion away from the muscularis into the centre of the lumen. Hot snaring is then undertaken with a safer margin between the mucosa and muscularis. There is good evidence to support this as an alternate or even primary option for EMR (128).

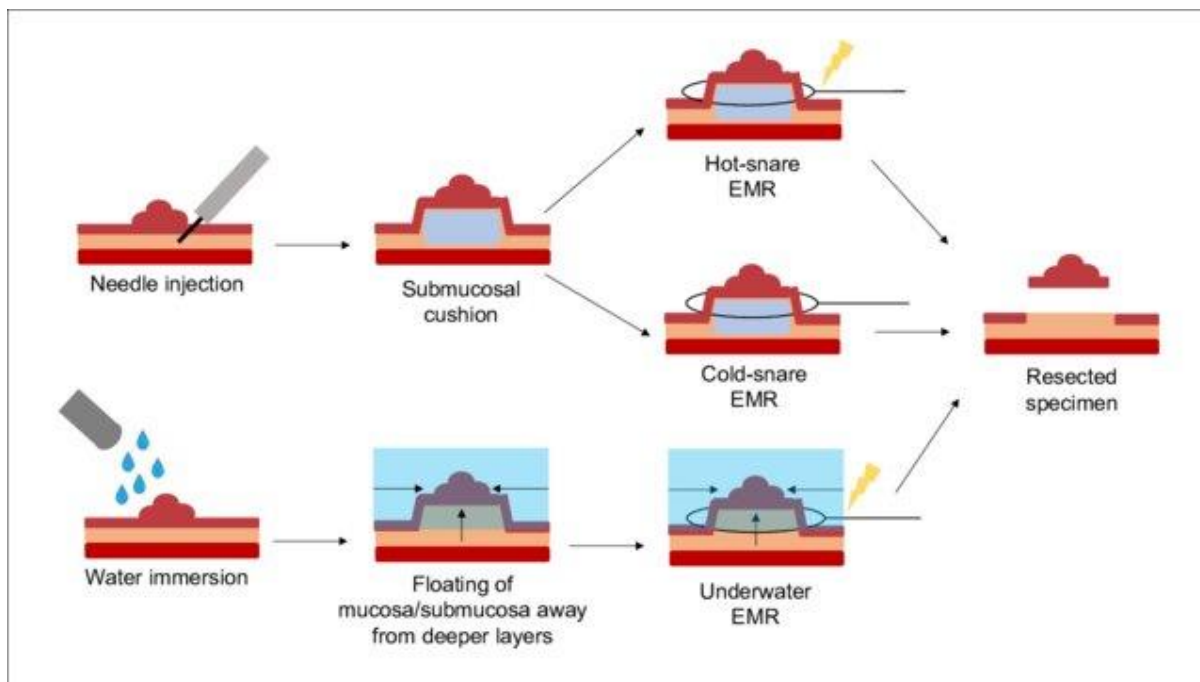


Figure 5.3 Endoscopic Mucosal Resection Techniques (lift with hot and cold snare, and underwater EMR)

5.2.4 Endoscopic Submucosal Dissection

Endoscopic submucosal dissection (ESD) uses a combination of submucosal injection and dissection of lesions en-bloc through use of electrosurgical knives. ESD is a prolific technique in the East with slower uptake in the West. However, Europe is now increasingly using ESD as a first line technique.

ESD involves the following steps (Figure 5.4) (129):

1. Marking: the tip of the knife is used for marking the margin for resection.
2. Injection: a solution is injected into the submucosa to elevate the mucosa.
3. Incision: an incision is made around the circumference of the lesion.
4. Submucosal dissection: the submucosa is dissected with care to avoid perforation.
5. Haemostasis: coagulation of bleeding vessels as required throughout.

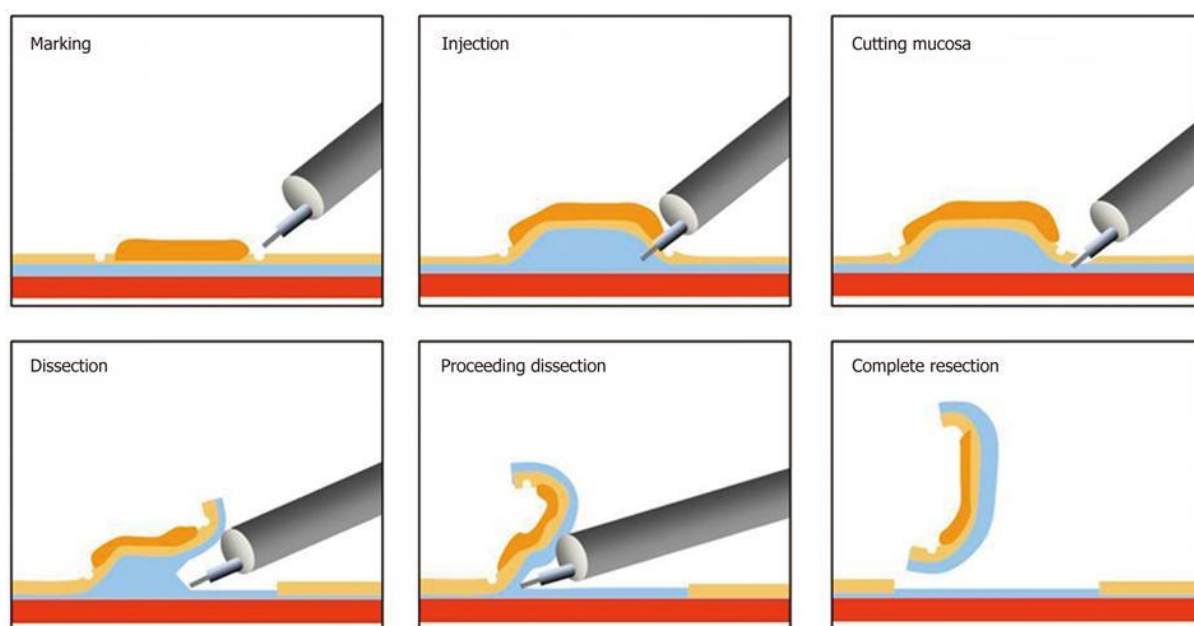


Figure 5.4 ESD technique

ESD was developed in Japan in the late 1990s as a reaction to the shortcomings of endoscopic mucosal resection (EMR) in removing large superficial gastric malignancies (130).

ESD is technically more challenging than EMR, with longer procedural times and higher rates of complications, but the *en-bloc* resection allows good histopathological assessment of lesion margins, lower recurrence rate and a greater minimally invasive potential for cure (131–133).

The procedure is well established in Asia but has been slow to spread into the West for a few reasons. These include lower availability of mentors for a technically challenging procedure and high complication rates. Hybrid ESD involves ESD combined with the snaring of EMR, simplifying the most challenging ESD step: submucosal dissection. This is associated with shorter procedure times and lower complication rates, but with lower *en-bloc* resection rates (134).

The European Society of Gastrointestinal Endoscopy recommends ESD be used first line in the removal of gastric superficial neoplastic lesions with very low risk of lymph node metastases. It is also recommended first line for superficial oesophageal squamous cell cancers. ESD can be considered in Barrett's related lesions for larger and poorly lifting lesions. For colonic and rectal lesions, ESD can be considered if there is a high suspicion of limited submucosal invasion (indicated by depressed morphology and an irregular or non-granular surface pattern) –

especially if >20mm, or in lesions that otherwise cannot be optimally and radically removed by snare based techniques (135).

There are multiple challenges faced by ESD practitioners. While the practice of ESD in gastric lesions is relatively well established and safe, the oesophagus with its narrow lumen and challenging workspace, and the colon with its tortuous course and folds are more challenging frontiers. The nature of performing this procedure endoscopically means that conventional methods offer no mechanism for providing counter-traction while performing dissection, impeding visibility and increasing the rate of complications. Traction methods, and assistive devices such as caps and hoods have been developed in an attempt to improve procedural visibility, stability and speed, and thus patient safety (136). In Japan, where the procedure is best established, the complication rates (including perforation, peritonitis and bleeding) are 3.5% for gastric ESD, 3.3% for oesophageal ESD and 4.6% for colorectal ESD(137).

5.3 Review of ESD tools available

5.3.1 Methodology

The terms ‘endoscopic submucosal dissection’ and ‘ESD’ were inputted into the search engines of PubMed, Embase, Medline, and Cochrane. Only articles available in English were included. The articles were then screened for relation to ESD. A total of 119 articles relating to accessories used in ESD, of which 85 were in the English language and relevant to the review are included. Articles excluded were those relating to experimental tools or techniques not available to the general practitioner, outdated articles and Cochrane trials that were never published.

5.3.2 Knives

There are a variety of products available on the knife market, and the field has evolved rapidly over the past two decades with efforts to improve efficacy, safety and cost-effectiveness (Figure 5.5) (136). In spite of this, the evidence differentiating them is sparse and choice often comes

down to operator preference. Image 1 shows some of the knives on the market, which will be discussed further here.

5.3.2.1 Needle-type

- Description: Sharp tip and monopolar current.
- Advantages: Simple, easy to use.
- Disadvantages: Poor control, risk of unintended tissue trauma (thus primarily used for making initial incision) – although somewhat overcome with ball-tipped knives (ball like process at tip behind which the knife can be retracted, can also use ball to stabilise on surface before cutting, e.g. Dual Knife).

5.3.2.2 Insulation-Tip (IT)

- Description: Insulator reduces risk of puncturing tissues and can be used for haemostasis.
- Advantages: More suitable for submucosal dissection than conventional needle-type knives.
- Disadvantages: Difficult to manoeuvre so sometimes requires dissection without direct visualisation of the lesion.

5.3.2.3 Hybrid/ Waterjet:

- Description: central lumen in knife through which fluid can be flushed for needleless injection.
- Advantages: Shorter procedure times than knives without waterjet function, faster submucosal injection, no need to change tools.
- Disadvantages: More challenging to use, more equipment required.

5.3.2.4 Scissor/grasping type

- Description: Scissor-style grasping grip with monopolar frequency that can cut the tissue being held.
- Advantages: Ability to grasp away from the submucosal plane and check position before cutting improves safety, good for more technically challenging anatomy e.g. oesophagus and colorectal as well as gastric (138–143).
- Disadvantages: The Clutch Cutter (Fujifilm, Tokyo, Japan) cannot make a sharp mucosal incision, whereas alternative SB knives struggle to control severe bleeding due to thin shape. An initial incision is still required by an ESD knife.

5.3.2.5 Others

- **Triangle tip/ TT Knife** (Olympus, Tokyo, Japan): diathermic disc at tip – allows for more detailed dissection at expense of procedure time.
 - o Triangle Tip Knife J has waterjet capacity.
- **Flex Knife** (Olympus, Tokyo, Japan; MTW, Wesel, Germany; Kachu, Seoul, South Korea): round tip with twisted wire of adjustable length (like a snare), soft nature reduces perforation risk but can attract carbonised particles reducing electrical current flow.
- **Hook Knife** (Olympus, Tokyo, Japan; MTW, Wesel, Germany): L-shaped hook that can cut horizontally and vertically, allowing for detailed dissection at expense of longer procedure time.
- **Fork Knife** (Kachu, Seoul, South Korea): two interchangeable knives (fixed flexible snare plus fork-shaped knife with inlet for injection/irrigation) – switched with knob allowing one knife to perform entire procedure.
- **Dissectors** (Karl Storz, Tuttlingen, Germany; Ovesco, Tübingen, Germany): perform blunt dissection to remove lesions.



Figure 5.5 Knives used in endoscopic submucosal dissection

From left to right: Needle Knife (Olympus, Tokyo, Japan), Dual Knife (Olympus, Tokyo, Japan), IT2 Knife (Olympus, Tokyo, Japan), Splash M Knife (PENTAX, Tokyo, Japan), TT knife (Olympus, Tokyo, Japan), Flex Knife (Olympus, Tokyo, Japan), Hook Knife (Olympus, Tokyo, Japan). Images taken with permission from Chun, 2017.

5.3.2.6 Evidence

There are a number of comparative trials between the various knives, primarily examining end points of procedure time, resection rate and risk of complications. However, the published evidence base is not broad with choice of tools guided through user experience and local unit practices (Table 5.1).

Two studies compare the Flush Knife with the Flush Knife BT, finding that the ball-tipped version is associated with longer time to initial bleeding and fewer points requiring the use of haemostatic forceps throughout the GI tract – although some authors have suggested the original Flush Knife may still be more suited to severely fibrotic lesions(144,145).

The Flush Knife has also been compared with the Flex Knife in colorectal ESD, finding that the Flex Knife was associated with longer procedure times, likely related to more device changes and increased fluid utilisation (146).

There are multiple further trials comparing hybrid knives with conventional non-waterjet knives (most commonly IT, Dual, Hook and Mucosectom knives) showing shorter procedure time with the hybrid knives (primarily related to fewer instrument changes) without any significant differences in adverse events (147–151). A further study of hybrid knives use in trainees found that initial performance (in terms of resection rate with clear margins) with hybrid knives is lower than with conventional knives, but the learning curve is short and associated with rapid improvement over the course of 50 procedures (152).

A 2016 trial comparing the Dual Knife with the IT knife nano for colorectal lesions found that the IT knife nano was associated with shorter procedure times and reduced perforation risk(153). There are also current trials looking at procedure time and outcomes of use of the IT knife nano in colorectal lesions >30mm both alone (154) and compared with the Dual Knife. In colorectal ESD, the Fork Knife has been compared with the Flex knife, finding that the Fork knife was associated with shorter procedure times (59.63 minutes vs 76.65 minutes) and higher complete resection rates (81.1% vs 73.6%) (155).

Numerous studies have compared the SB knives with the Hook Knife, and have shown that scissor-type knives have a similar or superior safety profile, with a shorter time to competency when used by novices(116,156–158) and similar results when compared with the Flush Knife(159). Further studies have compared the Clutch Cutter to conventional knives, with mixed results on whether the procedure time is shortened, prolonged, or not significantly different (141,160–163).

Knife Type	Brand Name	Manufacturer	Marking	Injection	Mucosal incision	Submucosal dissection	Haemostasis
Needle	Needle Knife	Olympus	x		x	x	
	Needle Controllable Knife*	MTW	x		x	x	
	Speedboat RS2	Creo Medical	x	x	x	x	x
Dual	DualKnife*	Olympus	x		x	x	x
	DualKnife J*	Olympus	x	x	x	x	x
	Splash-M knife*	PENTAX	x	x	x	x	x
IT	IT knife, IT2*, IT nano	Olympus			x	x	x
	Swanblade*	PENTAX				x	

	Mucosectom*	PENTAX				X	
	Ball ESD Knife*	MTW			X	X	X
Hybrid	HybridKnife* (I-type, T-type, O-type), HybridAPC	ERBE	X	X	X	X	X
	Flush Knife, Flush Knife BT (ball-tip), Flush Knife BTS* (ball-tip slim), Flush Knife NS*	Fujifilm	X	X	X	X	X
Scissor-type	SB Knife, SB Knife Jr	Sumitomo Bakelite	X			X	X
	3-in-1 SB Knife	Olympus			X	X	X
	Clutch Cutter*	Fujifilm			X	X	X
Hook	Hook Knife*	Olympus	X		X	X	X
	Hook Knife J*	Olympus	X	X	X	X	X
	Hook Knife*	MTW	X		X	X	X
Fork	Endo FS	Kachu	X	X	X	X	X
Blunt dissectors	EndoDissector	Karl Storz	X			X	X
	Endo-Maryland Dissector*	Ovesco	X			X	X

Table 5.1 A comparison of ESD knives and their functionalities

(* are those available to buy in the market in the UK)

Manufacturers: Creo Medical, *Chepstow, United Kingdom*; ERBE Elektromedizin GmbH, *Tübingen, Germany*; Fujifilm, *Tokyo, Japan*; Kachu, *Seoul, South Korea*; Karl Storz, *Tuttlingen, Germany*; MTW, *Wesel, Germany*; Olympus, *Tokyo, Japan*; Ovesco, *Tübingen, Germany*; PENTAX, *Tokyo, Japan*; Sumitomo Bakelite, *Tokyo, Japan*.

5.3.3 Distal Attachments

The attachment of a transparent cap to the end of an endoscope allows fixing of the endoscope at a constant distance from the mucosa to aid in visualisation of the lesion and thus help in reducing the risk of complications. Caps may come with holes for drainage of blood and water, and also of different shapes (e.g. straight, oblique) depending on the anatomy of the area in which they are being used (Figure 5.6) and user preference.

There is some evidence to suggest that cap-assisted EMR significantly shortens procedure time in comparison with EMR or ESD without a cap in removing rectal tumours (164,165). There are as yet no head to head trials comparing cap versus non-cap assisted ESD. Hoods are a type of cap with a tapered tip that can be used to elevate mucous membranes following the initial incision to aid with submucosal dissection. Again, comparative trials are not present, and evidence is limited to case studies(166).

The Endolifter (Olympus, Tokyo, Japan) is a cap with grasping forceps at the distal end which is able to lift the mucosa facilitating an easier dissection. This is a form of traction described further in the Traction Methods section. It has been shown to reduce procedure time, amount of submucosal injection and bleeding in pig models(167).



Figure 5.6 Distal attachments

Left: Caps (Olympus, Tokyo, Japan). Right: Endolifter (Olympus, Tokyo, Japan). Images taken with permission from Chun, 2017(136) and Jang, 2017(168).

5.3.4 Injection Solution

There are several fluids that are used to elevate the submucosa. Sodium chloride (0.9%) has the advantage of being cheap and is widely used for EMR, but it quickly absorbs into the surrounding tissue and ESD requires a more prolonged period of elevation(169). Solutions such as hypertonic saline (3-4.7%), dextrose (20/50%) and hydroxypropyl methycellulose provide a longer duration of submucosal lift, but can cause local inflammation with tissue damage due to its raised osmolality(170,171). Glycerol (10% glycerine plus 5% fructose) is a less inflammatory option, but has a tendency to generate smoke(172).

At the more viscous end is hyaluronic acid, which has a long lasting cushion and can be diluted, but is expensive and may stimulate the growth of any residual tumour cells (173–175). A randomised controlled trial comparing sodium alginate against hyaluronic acid showed non-inferiority of sodium alginate with regards to *en-bloc* complete resection and formation and maintenance of mucosal elevation, although a higher rate of adverse events(176). Eleview (Cosmo Pharmaceuticals, Dublin, Ireland) and ORISE gel (Boston Scientific, Marlborough, USA) are synthetic solutions specifically designed for colorectal endoscopic resection and have been shown to have excellent cushion-forming ability and to have a very long duration of lift. They also contain dye to improve visualisation and highlight tissue planes, but are expensive(177). Hydroxyethyl starch is an alternative that is reasonably safe and cheap as well as generating a long elevation duration(178). Of note, a meta-analysis of injection fluids including sodium chloride (0.9%), dextrose, glycerol, hyaluronic acid, hydroxyethyl starch as described above, as well as fibrinogen mixture, succinylated gelatin and mesna (a medication typically used to inactivate urotoxic metabolites of some chemotherapy drugs), found no significant differences between non-saline injection fluids in terms of *en-bloc* and complete resection rates – although the data on fibrinogen, hydroxyethyl starch and glycerol was limited(179).

5.3.5 Haemostasis

A major complication of ESD is bleeding; both interprocedurally and delayed. Prophylactic coagulation and rapid treatment are important for successful patient outcomes, and there are a variety of tools available.

All knives have at least a limited capacity for haemostasis on small bleeding points, depending on the generator setting used (see Generators section). As mentioned previously, ball tip knives typically have improved haemostatic efficiency compared with standard needle knives. Hybrid knives have been demonstrated to reduce the need for haemostatic devices and regular haemostasis compared with conventional knives. The Splash-M knife (PENTAX, Tokyo, Japan) was designed with a metal plate on its distal sheath to facilitate improved haemostasis(180). Most knives perform monopolar anticoagulation, which is versatile, quick and easy to use; conversely, bipolar anticoagulation – as seen in the Speedboat for example – can be more targeted and thus reduces the risk of thermal injury(181–183).

For larger vessels and associated bleeds, specific haemostatic devices may be necessary. Clips are not widely used for bleeding control in ESD because they can interfere with the procedure, and tend to be reserved for uncontrolled bleeding or at the end of dissection(136). More widely used are haemostatic forceps (Figure 5.7). These are similar to hot biopsy forceps, but have smaller clips and thus increased precision. The Coagrasper (Olympus, Tokyo, Japan) is a monopolar forceps while the HemoStat-Y (PENTAX, Tokyo, Japan) is bipolar (see Image 3). A comparison of the HemoStat-Y with endoscopic hemoclippping on non-variceal GI bleeding found a higher successful treatment rate with the Hemostat-Y (100% vs 78.2%) and a shorter time to haemostasis (6.8 vs 13.4 minutes)(184). However, we found no papers directly comparing different forceps against each other.

Argon plasma coagulation (APC) is a non-contact method of achieving anticoagulation by using ionised argon gas to conduct electrical current from a probe to the bleeding point. The advantage of not directly touching the tissue is a reduced risk of re-bleeding and perforation on removal of the probe. However, it can be more challenging to stop active large vessel bleeding compared with haemostatic forceps.

Prophylactic cauterisation of visible vessels in the floor of the wound has been suggested to reduce bleeding(185). Some practitioners take this a step further and also perform clipping. This has been suggested to be safe in some studies(186). However, increasing use of electrocoagulation in preventing bleeding is not without its risks; it is estimated around 7-8% of

ESD procedures are associated with coagulation syndrome – a transmural burn causing localised peritonitis that typically can be managed conservatively, although 0.1-0.4% of patients undergoing ESD may develop delayed perforation potentially requiring emergency surgery(187).

Various barriers have been marketed for preventing bleeding following anticoagulation in ESD. One such medical adhesive, COMPONT (Beijing Compont Medical Devices, Beijing, China), was trialled against conventional wound management in 171 ESD cases demonstrating significantly reduced postoperative bleeding and hospital stay(188). PuraStat (3-D Matrix Ltd, Tokyo, Japan), a transparent barrier that forms a gel coat inducing haemostasis, is currently undergoing clinical trials and it is hoped will provide a further alternative to thermal haemostasis(189).



Figure 5.7 Haemostasis devices

Left: Coagrasper (Olympus, Tokyo, Japan). Right: Hemostat-Y (PENTAX, Tokyo, Japan). Images taken with permission from Chun, 2017 (136).

5.3.6 Perforation Management

Another key risk of the ESD procedure is perforation. Risk estimates range from 0-6.9% in oesophageal ESD, 2.4-9.6% in gastric ESD and 1.4-20.4% in colorectal ESD (190–192). Perforation may be classified as immediate (i.e. seen during the procedure as a definite defect) or delayed (i.e. diagnosed after the procedure on radiograph or CT demonstrating pneumoperitoneum, usually following the complaint of abdominal pain).

The European Society of Gastrointestinal Endoscopy sets out recommendations for the management of iatrogenic endoscopic perforations, with an emphasis on managing endoscopically rather than surgically wherever possible because it is both feasible and limits

post-surgical adhesions, although they note that holes larger than 3cm are unlikely to be amenable to endoscopic management(193).

The use of nasogastric or nasoduodenal tubes to divert gastrointestinal fluid (in oesophageal/gastric perforations), and the switching from air to carbon dioxide for insufflation to reduce risk of tension pneumothorax/pneumomediastinum may be appropriate. Small defects can generally be treated by clips. Through the scope clips will usually suffice for defects less than 1cm in diameter, while over the scope clips (or endo-looping plus clipping if not available) should be considered for holes less than 2cm. This management is successful in >90% of cases, avoiding further surgical management(194). Endoscopic suturing devices, such as the Overstitch (Apollo Endosurgery Inc, Austin, USA) may be used for larger luminal defects with success rates of >95% – however, such devices currently require a double channel endoscope and high operator skill level(195). For suspected delayed perforation, a computed topography (CT) scan is recommended. A normal CT should be treated conservatively with observation, as should extraluminal air without extravasation in duodenal perforations. Otherwise, surgical input should be sought.

5.3.7 Generators

The modern generators that are required for ESD have multiple power settings and have both monopolar and bipolar capabilities.

ERBE Elektromedizin GmbH (Tübingen, Germany) manufactures the ICC series as well as the VIO 300D. Cut modes include Auto Cut (standard), Endo Cut (with some coagulation effect - better for fibrosis/strictures(196)) and Dry Cut (high power mode for faster cutting). Coagulation modes include Swift Coag (similar to Dry Cut with more haemostasis), Forced Coag (higher voltage – can be used for submucosal dissection), Spray Coag (non-contact surface coagulation with low penetration – good for post procedure haemostasis) and Soft Coag (low voltage resulting in coagulation only with no cutting).

The ESG 100 (Olympus) has three standard monopolar cutting modes as well as PulseCut Slow and PulseCut Fast (equivalent to Endo-Cut). It has three monopolar coagulation modes (Soft

and Forced 1 and 2). It also has three bipolar cutting modes, and three coagulation modes (Soft, RfCoag and RfCap). RfCoag is a form of controlled coagulation with acoustic resistance feedback and an automatic end of procedure detection. RfCoag and RfCap are particularly suited for deep tissue coagulation without significant tissue destruction.

5.3.8 Traction methods

One issue with ESD in comparison with conventional surgery is that the entire procedure is performed through a single endoscope, and thus there is no second “hand” to provide traction on the submucosal layer after cutting and thus there can be difficulties visualising the dissection plane. There are various traction methods that have been developed to apply external traction in an attempt to overcome this, and various studies have shown these methods to be faster with higher rates of resection and lower rates of complications(197).

One of the simplest traction methods involves a silk line tied to a clip attached to the edge of a lesion, and then the lesion pulled proximally using the line. The advantages of this method is its simplicity, the lack of need for specialist equipment, and its versatility across oesophageal, gastric and colorectal lesions(198,199). However, it does require reinsertion of the scope, and traction can only be applied by pulling(200). The internal traction method modifies this somewhat, by attaching a band, ring or nylon to a clip attached to the lesion as well as a second clip on the opposite side. No re-insertion of the endoscope is required for this, and there is good evidence supporting its use in colorectal lesions(201,202). However, it does require more space and may not translate well to smaller working spaces, oesophageal lesions for example.

A method of traction that allows both pushing and pulling is the external forceps method, whereby external forceps gripped by second forceps inserted into the accessory port and anchored to the edge of the lesion. It has been shown to be effective in gastric and rectal lesions, although not in the deep colon and has the potential to cause injury(203,204). The Endolifter (Olympus, Tokyo, Japan) described in the caps/hoods section works in a similar way. Another such method allowing both pushing and pulling is the clip and snare with pre-loop, in which the endoscope is withdrawn and a snare pre-looped around the distal end. A clip is inserted through the port to grasp the mucosal flap, then the snare is moved along forceps to the clip to grasp the

mucosa and the clip is released. There is some evidence for its use in gastric lesions, and can be used in the colon with a balloon overtube (205,206).

A further technique that allows traction in any direction is the double endoscope method, whereby a second smaller endoscope is inserted alongside the main scope with grasping forceps. However, this clearly requires a lot of space, and so far is useful only in gastric and rectal lesions(207). For rectal ESD, another method generating excellent traction for rectal lesions is the GelPOINT (Applied Medical, Amersfoort, Netherlands), whereby a transanal access port is created for the endoscope, plus two retractors passed by a laparoscopic surgeon – although clearly this method requires a lot of manpower. The ORISE Tissue Retractor System (Boston Scientific, Marlborough, USA) is an overtube with two separate flexible channels, down which graspers can be deployed, allowing independent traction in a separate plane to the endoscope – however, it is relatively new with little real world use so far(208).

Other potential traction methods include magnetic traction (magnet placed internally and manipulated using an external magnet), which has shown promise in animal models, but concerns remain with regards to usefulness in obese patients as well as interaction of the magnet with patient blood vessels and equipment(209).

5.4 Conclusion

Endoscopic submucosal dissection is an advanced technique with multiple technical challenges. A wide range of tools are available and more continue to be developed in an attempt to speed up procedure times and reduce complications. However, it is currently limited to the expert endoscopist, and comparative studies, particularly in non-knife tools, are limited in number. This means selection often comes down to clinician preference with evidence of efficacy from clinician user experience and case reports. Evolution of the ESD toolbox will make the procedure increasingly accessible to more endoscopists. As the number of ESD practitioners increase, expert experience cannot be solely relied on, and a more substantial evidence base will be required to evaluate efficacy and safety of the multitude of tools.

6. Endoscope Control Systems and the Rise of Robotic Endoscopy

Content from this Chapter was Published in (66):

Sivananthan A et al. The evolution of lower gastrointestinal endoscopy: where are we now?. *Ther Adv Gastrointest Endosc.* 2020;13:2631774520979591. Published 2020 Dec 20. doi:10.1177/2631774520979591

6.1 Background

Successful endoscopy is both reliant on the endoscopist skillset and the endoscope technology itself. The ability of the endoscopist to accurately steer the endoscope is critical to successful endoscopic therapy. The basic endoscope control system has changed little over the last 50 years, centred on the 2 steering knobs attached to antagonistic cables at the endoscope tip. As the therapeutic remit of endoscopy widens, the need for high fidelity control of the instrument also increases to allow the precise control required of advanced therapeutic endoscopy alongside the cognitive workload on the operator.

The aims of this chapter are to:

1. Outline the anatomy and control system of the current endoscope
2. Explore the challenges of the current endoscope control system
3. Review robotic endoscope control platforms

6.2 The Current Endoscope and Control System

6.2.1 Endoscope Anatomy

The modern endoscope is divided into three sections; the control section, the insertion tube (including the endoscope tip) and the connection section (Figure 6.2) (210).

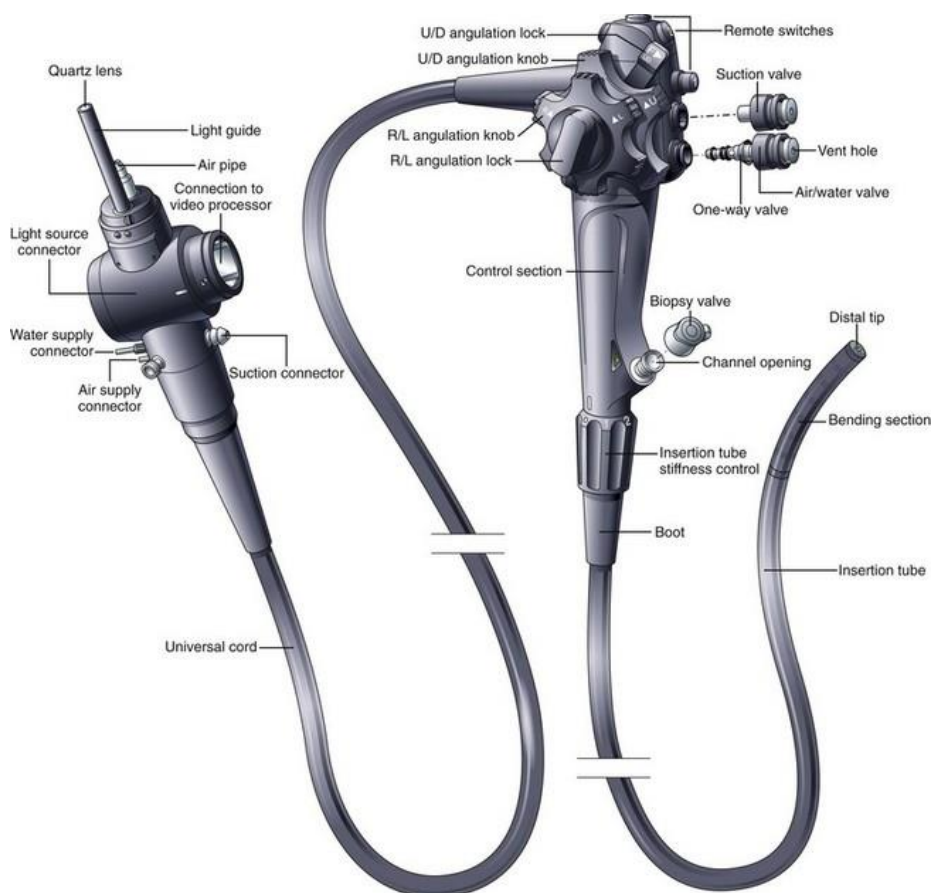


Figure 6.1 Endoscope divided into connection section, control section and insertion tube (left to right)

6.2.1.1 The Connection Section

The connection section bridges the endoscope and main stack allowing transmission of the light source down the endoscope and images up the endoscope. In addition, suction, air and water delivery to the main body are transmitted through this connection.

6.2.1.2 The Insertion Tube

The insertion tube must both be flexible and rigid as required by the endoscopist. Key components of the endoscope must also be housed here to reach the endoscope tip and main stack. The endoscope houses the light fibres to illuminate the lumen down the endoscope and the CCD signal wires to transfer the image back to the endoscopy monitor. Four angulation wires allow steering of the endoscope tip through antagonistic cables. The air, suction, water and instrument channels are also housed (Figure 6.3) (210).

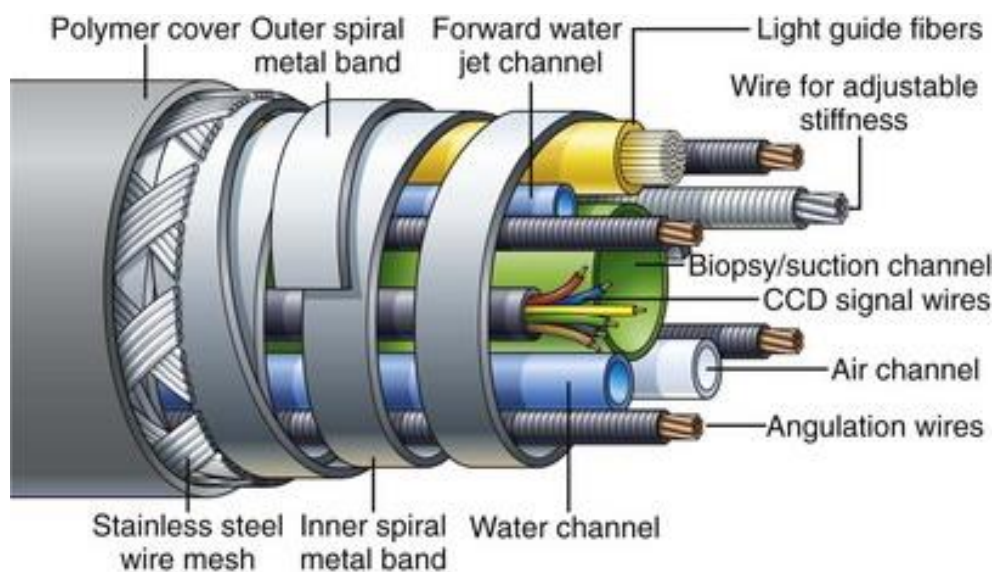


Figure 6.2 Internals of the insertion tube

An adjustable stiffening wire allows control of the stiffness of the endoscope stiffness controlled by the stiffness control ring within the control section (Figure 6.4) (211).

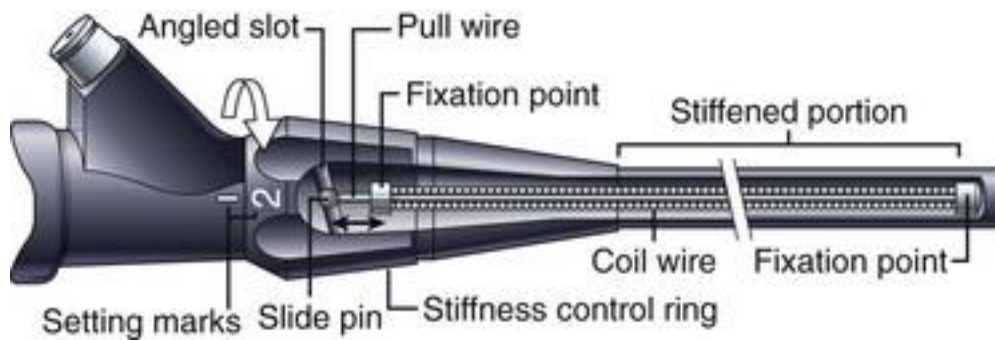


Figure 6.3 Variable stiffness control in an endoscope

6.2.1.3 The Control Section

The control section is held in the left hand and houses numerous controls for the endoscopist. The angulation knobs allow endoscope steering of the tips. The buttons and valves allow delivery of water, air and suction through the endoscope channels. Additional buttons may allow, photo capture, image enhanced views and adjustment of the scope guide orientation. In the control section there is also access to the instrument channels for delivery of endoscopic instruments (Figure 6.5) (212).

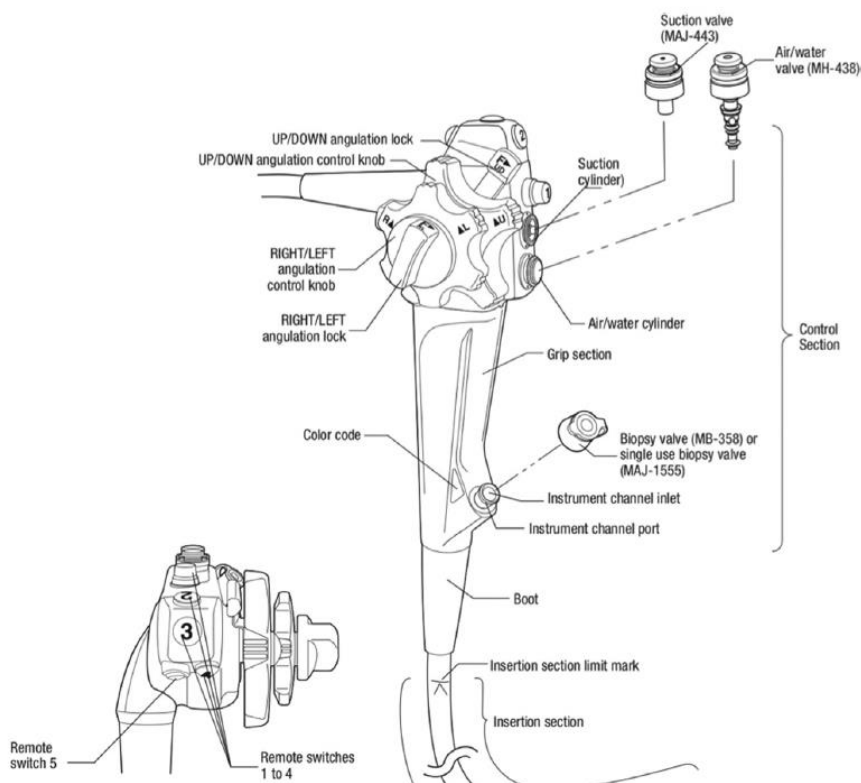


Figure 6.4 Endoscope Control Section

6.2.1.4 Tip Control

Two degrees of freedom are provided by the angulation knobs. The endoscope tip is flexible through a series of rings with 4 angulation wires. Each angulation knob is connected to two wires.

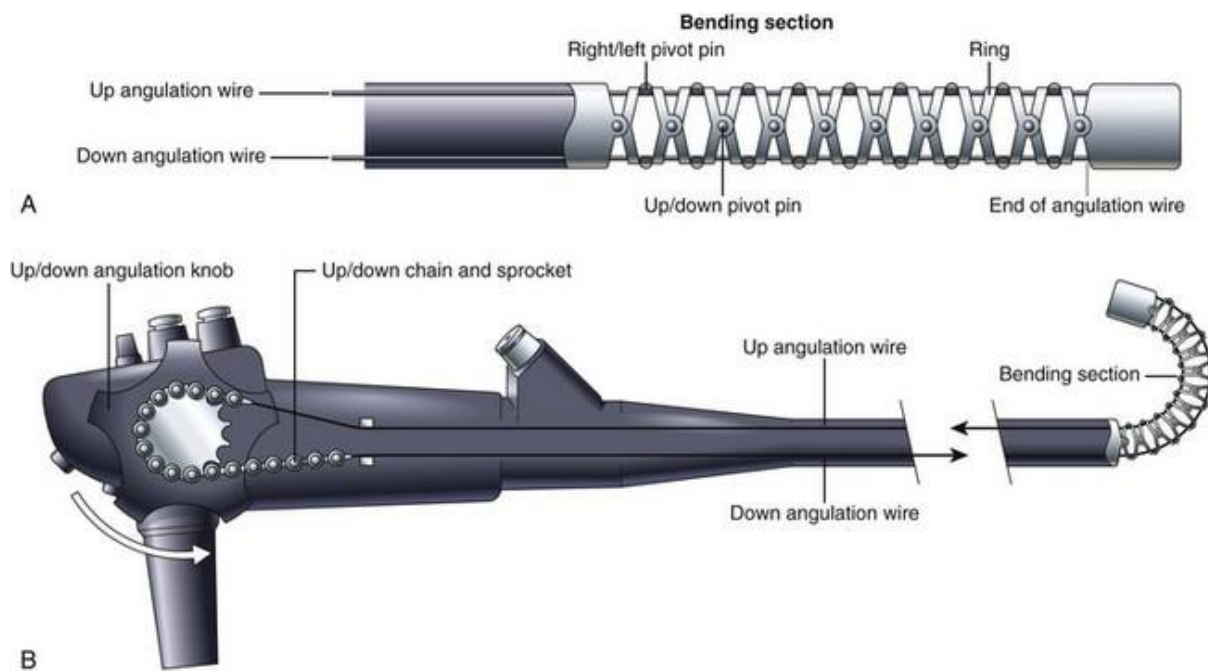


Figure 6.5 Bending section of endoscope with angulation knobs and wires.

The large up/down knob is attached to the angulation wires connected to 12 o'clock and 6 o'clock of the tip. Clockwise rotation of the knob pulls the 6 o'clock angulation wire taut and loosens the 12 o'clock wire curving the distal tip to the 6 o'clock position. Anti-clockwise rotation produces the opposite effect with resultant up angulation towards the 12 o'clock position (Figure 6.7 and 6.8) (213) (102).

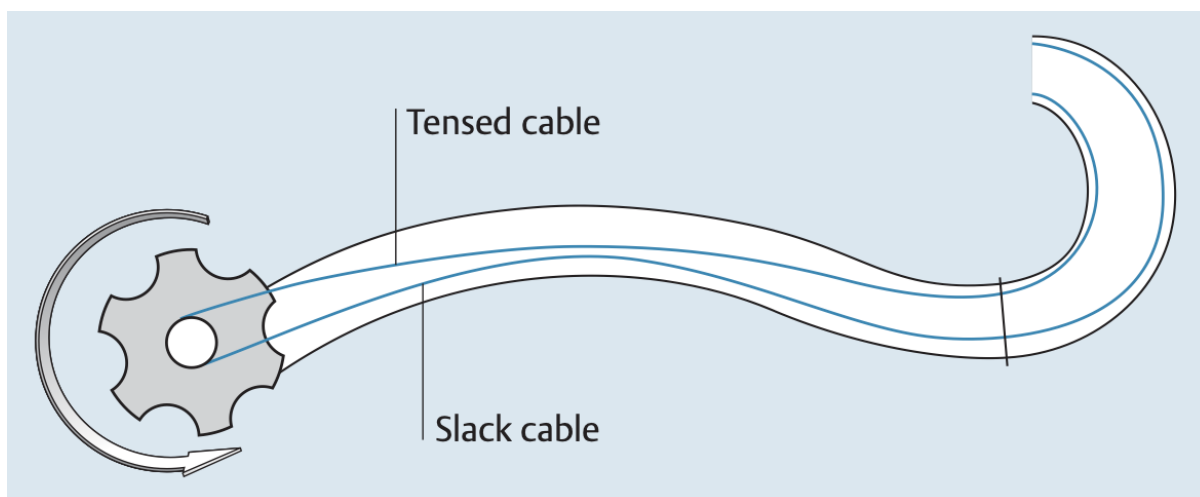


Figure 6.6 Antagonist cables running from steering wheel to endoscope tip



Figure 6.7 anticlockwise rotation of the big knob (left) and clockwise (right) producing tip deflection up and down respectively.

The small outer knob is attached to angulation wires in the 3 and 6 o'clock position allowing tip deflection to the left and right (Figure 6.9).



Figure 6.8 anticlockwise rotation of the small knob (left) and clockwise (right) producing tip deflection left and right respectively.

6.2.1.5 Endoscope Control

There are 4 degrees of freedom of control within the standard endoscope. In addition to the knob steering; insertion and withdrawal provide one degree of freedom. Torque of the endoscope (clockwise and anticlockwise rotation of the scope) performed manually by the right hand holding the insertion staff provide a second degree of freedom. All of these degrees of freedom are used together for endoscope steering.

6.3 Challenges of the Current Endoscope Control System

6.3.1 Hysteresis and Force Transmission.

Delivery of force and control of instruments down a curved endoscope is a well-documented challenge in endoluminal surgery. The friction between the instrument and the instrument channel, the degree of curvature of the scope in the lumen and the flexibility of the instrument itself all compromise delivery of the operator force input to the instrument (214–218). This phenomenon of delayed transmission is known as hysteresis. For the endoscopist this phenomenon results in a delay of both endoscope and instrumentation control. For example small steering adjustments may have variable delays in actualisation. Force delivery of needles,

knives or snares will be reduced and delayed. Advanced endoscopic therapy requires high fidelity and precision movements which is compromised by hysteresis. Laparoscopic surgery uses rigid instruments which allow direct force delivery of operator input to end effector output. Research shows a significant reduction in push and lateral force through flexible instruments versus laparoscopic instruments (219,220).

6.3.2 Triangulation

Triangulation involves the use of two separate instruments brought into the field of camera view to allow accurate tissue interaction and control (221). Endoscopic triangulation in a conventional flexible endoscope is compromised by endoscopic instrument channels being parallel and extremely close to each other. In addition the endoscopic view and instruments all move together as opposed to laparoscopic triangulation where they can be moved independently of each other allowing better visualisation and manipulation of the tissue (222–224).

6.3.3 Workload

Endoscopy training has a well-documented steep learning curve attributable to the non-intuitive control system as detailed prior. The non-intuitive endoscope control has an associated high cognitive workload (225). Endoscope steering and repositioning required multiple combinations of movements of the 4 degrees of freedoms of the endoscope (tip steering, torque steering and endoscope insertion and withdrawal). The inputs required are also continuously variable dependent on the flexible endoscope configuration which may encompass endoscope loops.

Therapeutic endoscopy requires high fidelity precision movements through this control system. Most commonly endoscopes have only one therapeutic channel and instruments must be continuously changed. The conventional endoscope control system is bimanual and therefore instrumentation is performed by an assistant requiring effective communication and adding another step susceptible to human error. If the endoscopist needs to perform instrumentation themselves, they must rely on an assistant to hold the endoscope adding a further potential error

susceptible step. This introduces a significant barrier to therapeutic endoscopy skill acquisition (226).

6.4 A Review of Current Robotic Endoscope Platforms

The endoscope control system has barely changed since 1970 still reliant on antagonistic cable steering of the endoscope tip. As the endoscopic therapeutic remit evolves the barriers of this control system are becoming more apparent. Collaboration with the engineering community as engendered exciting novel robotic endoscope control systems.

Robotic control systems have been designed to aid overall endoscope locomotion mainly aimed at easier insertion by the endoscopist, higher rates of completed endoluminal examination and reduced pain for the patient. More complex robotic systems have been designed to allow intuitive endoscope insertion, endoscope repositioning and instrument control to allow fully robotic therapeutic endoscopy.

6.4.1 Robotic Driven Locomotion Endoscope Platforms

6.4.1.1 Motorised Spiral Endoscopy (MSE) – Power Spiral (Olympus corp., Japan) (24):

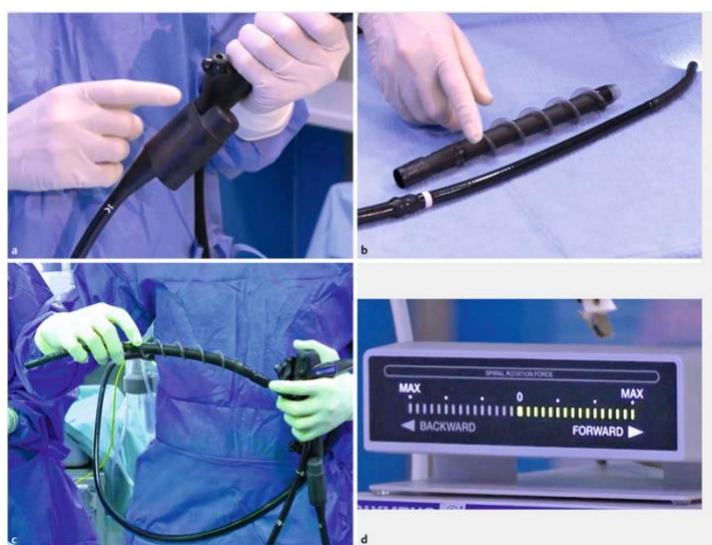


Figure 6.9 Power Spiral (Olympus corp., Japan)

Balloon enteroscopy and video capsule endoscopy have been the preferred modalities to examine the small bowel mucosa (227). Spiral enteroscopy allows for deep enteroscopy through the continuous corkscrewing motion of the endoscope tip pleating of the bowel (228) and therapeutics to be done at the same sitting. A meta-analysis comparing spiral enteroscopy (the two-person controlled Spirus Medical Endo-Ease Overtube) versus balloon enteroscopy showed similar diagnostic and therapeutic outcomes but with shorter procedural times (mean reduction of 11.26 minutes, $p=0.010$) (229).

Olympus developed POWER SPIRAL (Olympus, Japan) (Figure 6.10) in 2015; a single operator spiral enteroscope with a built in rotating motor, a disposable short overtube with atraumatic soft spiral fins, foot pedal controls and a visual force gauge (230). A recent small prospective clinical trial in 30 patients showed 100% success in anterograde enteroscopy (beyond the ligament of Trietz) and retrograde enteroscopy (proximal to the ileocaecal valve) with 70% total enteroscopy rate. There was a 20% adverse event rate (mucosal tears, jejunal haematoma and oesophageal erosion) but no serious events occurred (231). A feasibility trial looking at the use of MSE in colonoscopy demonstrated a caecal and terminal ileal intubation rate of 96.7% with an ADR of 46.6%. The soft fins theoretically flatten mucosal folds on withdrawal to increase lesion detection (230). The potential for improved caecal intubation rates and better visualisation, with single operator spiral intubation, is potentially interesting but need further validation (232).

6.4.1.2 Aer-O-Scope (GI View Ltd, Israel) (233):

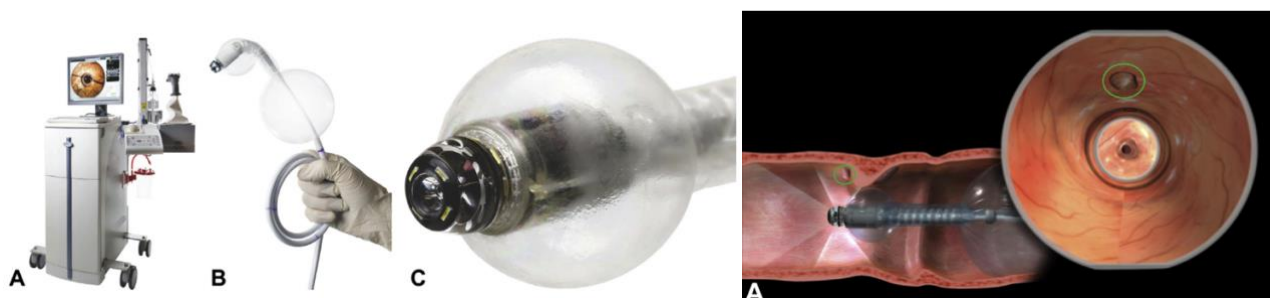


Figure 6.10 Aer-O-Scope (GI View Ltd, Israel)

Aer-o-scope (GI View Ltd, Israel), CE marked and FDA approved(234), (Figure 6.11) was designed to improve visualisation, reduce perforation, improve comfort, decrease infection risk, and reduce the learning curve for operators (233).

The novel platform is a joystick controlled disposable pneumatic self-propelling and navigating endoscope. The endoscope has a rectal balloon and hourglass shaped scanning balloon. Both balloons are inflated on insertion creating an airtight seal between them. A computer algorithm inflates the space with carbon dioxide creating positive pressure and thus gentle propulsion of the proximal scanning balloon. Pressure exerted by the endoscopist is dissipated over the balloons which are hydrophilic coated to lower friction resulting in colonic wall pressure of 60mbar vs the 1200mbar that can be seen in conventional colonoscopy (233).

The fully steerable tip contains a high definition camera with 57 degrees field of view anteriorly and a novel 'omniview' 360-degree camera that allows panoramic views behind haustral folds. The tip contains a LED light source with irrigation, suction and a recently introduced therapeutic channel (235).

Aer-o-scope has achieved caecal intubation rates of 98.2% but only visualised 87.5% of polyps seen on conventional colonoscopy. This was despite a 94.9% lesion recognition on a simulated double blinded porcine study (235). Caecal intubation took a mean of 13:38 minutes. Operators became proficient in this technique after 8 to 10 procedures (233). The latest version is anticipated to be released at a cost of \$250 for the disposable section and \$15,000 for the non-disposable platform. Conventional reusable colonoscopes range from \$80,000 to \$120,000 and reprocessing costs between \$140 and \$280. Disposable endoscope cost benefits are potentially attractive and disruptive (236).

Its novel mechanism has potential benefits for patient tolerability, endoscope reprocessing costs and polyp detection. Further evaluation is required to validate these claims and the low polyp detection rate must be interrogated and improved upon.

6.4.1.3 Endotics (Era Endoscopy, Italy) (237):



Figure 6.11 Endotics (Era Endoscopy, Italy)

Endotics (Era Endoscopy, Italy) (Figure 6.12) is a self-propelled, joystick-controlled endoscope. It consists of a disposable probe with a steerable tip and flexible body, 3mm working channel, a specialised electro-pneumatic tank and a separate workstation allowing handheld control with a joystick. The probe contains a camera with conventional LED light source, water and an air channel. The probe head is steerable 180 degrees in all directions. Endotics has a novel semi-automatic self-propulsion mechanism. The probe advances using a semi-automatic sequence based on the inchworm. The probe can clamp onto the mucosa through both vacuum and mechanical grasping.

A simulated study with a porcine colon and load sensors showed a 90% reduction in stress pattern versus standard colonoscopy. A trial in 40 patients showed a significant reduction in pain and discomfort scores versus conventional endoscopy (0.9 and 1.1. versus 6.9 and 6.8 respectively) (238).

In a cohort of patients with clinical or familial risk of polyps and carcinoma Endotics showed a 93.3% sensitivity and 100% specificity for the detection of polyps (239).

Early experimentation showed initially poor caecal intubation rates; 27% in 2009 (238) and 81.6% in 2010 (239). A retrospective study however showed a 93.1% caecal intubation rate with Endotics in 276 patients with failed caecal intubation on conventional colonoscopy (240).

The CE marked Endotics system is commercially available (241). It may serve a role in failed conventional colonoscopy with the additional benefits of a working channel to allow therapeutics, a disposable probe (preventing infection and reducing the associated costs and issues with endoscope reprocessing) and a user-friendly ergonomic design (reducing the learning curve).

6.4.1.4 Invendoscope (Ambu, Denmark) (242):



Figure 6.12 Invendoscope (Ambu, Denmark)

The CE marked and FDA cleared (243) Invendoscope (Ambu, Denmark) (Figure 6.13) is a single use ergonomically designed colonoscope. The former self-propulsion inverted sleeve mechanism seen in Invendo SC20 was abandoned. The current iteration, Invendo SC210, has a hydraulically actuated tip with electromechanical actuation rather than the more traditional Bowden cables (242). The tip can deflect in 180 degrees in all direction within a small working radius of 35mm (244). The tip houses a HD camera with suction, irrigation and 3.2mm working channels.

The endoscope is controllable by a detachable gamepad style joystick controller. This handheld controller purports to have a better ergonomic design which will reduce the musculoskeletal burden on the endoscopist (245).

An early feasibility study in 2011 with the Invendo SC20 showed a caecal intubation rate of 98.4% and a median time to caecum of 15 minutes. Sedation was only needed by 4.9% (246). More recently the SC210 underwent a feasibility study in 40 patients with a caecal intubation rate of 95%, time to caecum of 14.23 minutes and no major complications (247–249).

The cost of the disposable component is \$350. The Invendoscope offers potential cost benefits in scope acquisition and reprocessing costs. It purports ergonomic benefit to the user and reduction in discomfort to the patient. The authors of the recent feasibility study acknowledge that comparative study against conventional colonoscopy is now needed (247–249).

6.4.2 Robotic Driven Endoscope Locomotion and Instrumentation Platforms

6.4.2.1 Endoluminal Assistant for Surgical Endoscopy (EASE) (ICube laboratory, France) (250):

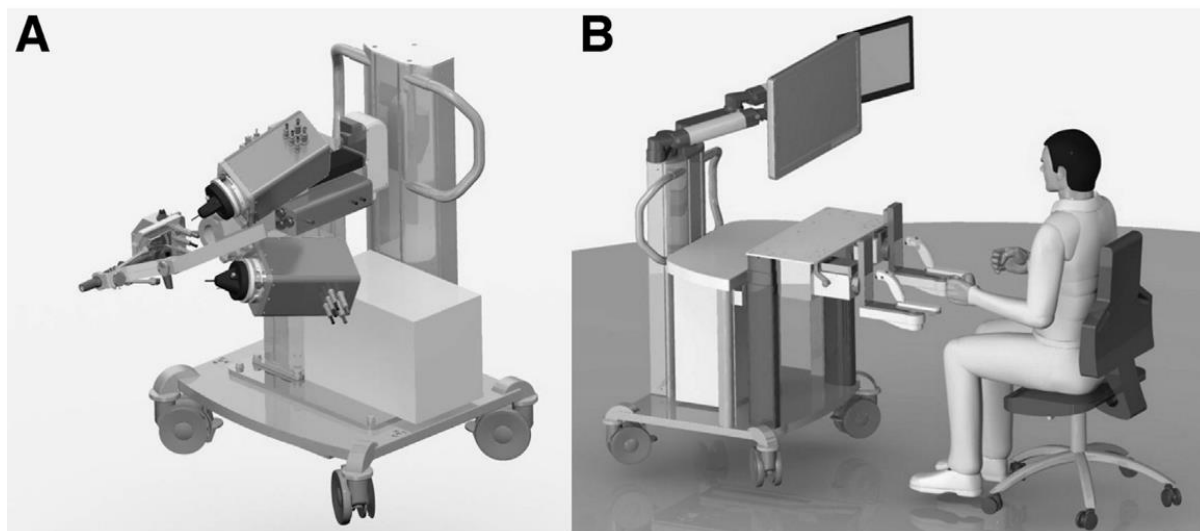


Figure 6.13 Endoluminal Assistant for Surgical Endoscopy (EASE) (ICube laboratory, France) (250)

EASE (ICube laboratory, France) (Figure 6.14) is a single user teleoperated master slave system. The EASE platform initially began as the two person operated Anubiscope (251); a tulip shaped distal cap facilitated atraumatic insertion which opened at the target site to reveal two flexible arms with four degrees of freedom (252) allowing a larger operative field (253). Anubiscope developed into the teleoperated STRAS system (Single-access Transluminal Robotic Assistant for Surgeons). Legner et al completed 12/18 porcine colorectal ESDs with version 1 (254) and

Zorn et al completed 12/12 porcine colorectal ESDs with version 2 (255). The Endoluminal Assistant for Surgical Endoscopy (EASE) is the most current iteration. The master controller consists of joysticks, thumb switches and triggers with two screens. (250). The slave component consists of a cart containing actuation equipment connected to a 53.5cm detachable endoscope. There are two 4.3mm channels down which a variety of teleoperable instruments can be delivered and a 3.2mm channel for conventional instruments to be deployed.

A non-randomised animal trial was conducted with a laparoscopic surgeon with no ESD or robotic experience using the EASE system and an expert endoscopist with over 1000 ESDs performing conventional ESD on porcine colonic pseudotumours. The robotic group achieved a 100% en bloc resection rate with a significantly reduced perforation rate (5 vs 33%) and total procedural time (33.36 vs 47.38 minutes; $P=0.011$)(250).

This is a powerful demonstration of a robotic platform allowing quicker, safer and more successful endoluminal surgery to be performed by a novice versus current benchmark techniques performed by an expert. Further work will be needed before in vivo trials are possible.

6.4.2.2 I²Snake (Hamlyn Centre, London) (256):

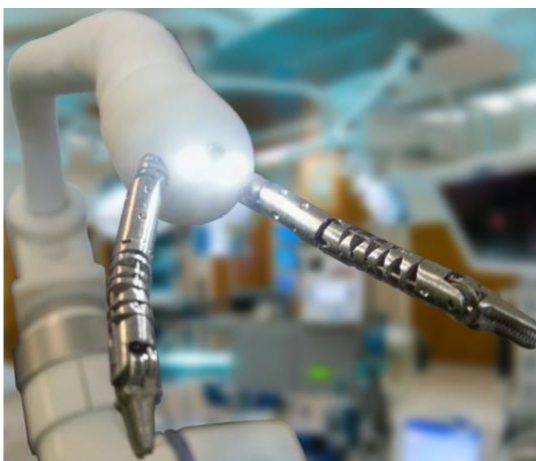


Figure 6.14 I²Snake (Hamlyn Centre, London)

The I²Snake (Intuitive imaging sensing navigated and kinematically enhanced robot, Hamlyn Centre, London) (Figure 6.15) is an evolution of the isnafe platform; a multi-articulated device activated by embedded micromotors and local tendons with a flexible neck actuated by two

pairs of antagonistic tendons. This was held by a robotic arm giving 7 degrees of freedom. Benchtop trials suggested more accurate control of tip movement versus conventional endoscopy (257).

I²Snake's body consists of thirteen 3D printed steel vertebrae, divided into three sections, with orthogonally arranged rolling joints which are steel tendon driven. This allows benchtop manipulation forces of 5.6N (258) and seven degrees of freedom and a broad range of configurations including S shapes and retroflexion, biomimicking a snake. There are 4 channels allowing deployment of a camera and light source, two 3.8mm diameter instruments and suction and irrigation and incorporated graspers which are also externally actuated with 5 degrees of freedom. Movements of the device and instruments are controlled with two electromagnetically tracked hand grippers with motion scaling to increase precision(256). External tendon actuation has issues with 'backlash hysteresis' but AI based software to compensate for this is being developed (259). Future ex vivo trials are required.

6.4.2.3 Endomaster EASE system (EndoMASTER Pte, Singapore)

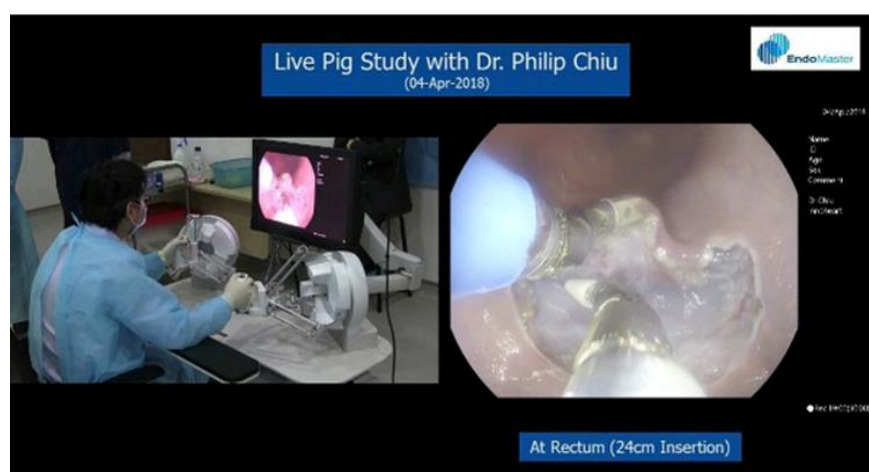


Figure 6.15 Master (EndoMASTER Pte, Singapore)

The Master and Slave Transluminal Endoscopic Robot (MASTER, EndoMASTER Pte, Singapore) (Figure 6.16) was a master slave platform initially designed for NOTES procedures (260) but pivoted into ESD. Early versions had a cable and motion sensor hand-controlled master device with haptic feedback. The slave system consisted of a grasper and electrocautery hook with

elbow and wrist joints, allowing 7 degrees of freedom. These were mounted externally onto a conventional dual channel endoscope. The instruments were externally actuated through tendon sheaths running through the instrument channels allowing manipulation forces of 3-5N(261). Two operators were required (262), the tools were fixed and an overtube was required for use. Initial feasibility studies showed success in porcine hepatic wedge resection (263), gastric ESD (264) and gastric full thick resection(265). A human feasibility study was successful in achieving R0 resection in 5 patients with gastric ESD with no complication and a mean dissection time of 18.6 minutes (266). A small trial demonstrated comparable results between novices and non-experts when using MASTER for ESD and a short learning curve for novices(267).

The most recent iteration, the Endomaster EASE system, has a purpose built 'slave' flexible endoscope with 2 instrument channels down which a variety of cable actuated robotic instruments can be deployed interchangeably with 7 DOF. A recent preclinical feasibility live porcine trial showed 100% (5/5) en bloc resection in porcine colorectal ESD without serious adverse events (268).

The Endomaster Platform shows exciting promise but currently has no CE nor FDA approval. (237).

6.4.2.4 Flex Colorectal Drive (Medrobotics, Corp, United States) (269):



Figure 6.16 Flex Colorectal Drive (Medrobotics, Corp, United States)

The Flex Robotic System (Medrobotics, Corp, United States) (Figure 6.17) is a single operator endoluminal surgical platform that was originally designed for head and neck surgery. The endoscope has a two concentric overtube system made up of multiple segments that articulate at a single point. The outer tube advances first with the inner tube following. The endoscope is flexible on insertion but can be stiffened in a non-linear shape to provide a stable base for intervention (270). A range of flexible wristed instruments pass down two accessory channels mounted on the sides of the endoscope(245). They are controlled like laparoscopic instruments allowing direct mechanical feedback. This differs to the electro-mechanically decoupled master-slave systems seen in other robotic platforms such as EASE, i-SNAKE and Endomaster EASE (269).

A multicentre, prospective single armed trial showed success in transoral oropharyngeal surgery. Access and visualisation of the intended lesion was successful in 95% (75/80) with successful surgery in 91.1% (72/79) (271). A human cadaveric trial showed feasibility of FLEX for transanal total mesorectal excision (taTME) (269). A retrospective case series of rectal local excision in 11 patients with Flex Colorectal Drive showed successful R0 resection in 10 of the patients with one case being abandoned due to poor patient positioning rather than robot error (272).

A recent study compared Flex assisted ESD with traditional ESD by 5 inexperienced operators (<5 ex vivo conventional ESD). 100% en bloc resection was completed with FLEX (10/10) and 50% with conventional ESD (5/10, $p<0.0001$). The total procedure time was significantly lower (34.1 vs 88.6 mins) in the FLEX group and there was a trend towards higher perforation rate ($p=0.18$) in the traditional ESD group. Technical workload (using NASA TLX scores – a quantitative scoring system of workload) was also significantly lower in the FLEX group (28.4 vs 47) (273).

FLEX colorectal drive has great potential in endoscopic intraluminal and transluminal surgery. It was cleared for use by the FDA in 2017. It currently only has a 25 cm reach. Increasing the length of the device is an exciting prospect.

6.4.2.5 Cyclops (Hamlyn Centre, London) (274):



Figure 6.17 Cyclops (Hamlyn Centre, London)

CYCLOPS (Hamlyn Centre, London) (Figure 6.18) is a bimanual robotic platform that can be fitted onto a conventional endoscope to facilitate ESD. A collapsible scaffold allows insertion of the endoscope and subsequent deployment of the system when the point of therapy is reached(274). This is covered in a soft silicone sleeve for insertion. Two 4mm aluminium overtubes contain the deployed instruments. A network of tendons, 6 pairs, actuate the overtubes and thus the instruments allowing 5 degrees of freedom(275). These in turn are actuated via Bowden cables by an external motor unit.

This novel use of parallel robotics allows high manipulation forces of 46 newtons, significantly higher than seen in many other robotic platforms. The operator controls the system through two haptic feedback Geomagic® Touch TM controllers. An early prototype showed a mean error of only 0.217mm during an ellipse tracing task (276).

Benchtop ex vivo trials showed a significantly quicker dissection time in simulated ESD in chicken fillets when using cyclops versus conventional ESD techniques. In vivo trials are underway. (275).

Cyclops has several advantages over comparative platforms including its compatibility with conventional endoscopes, its novel parallel robotic actuation method delivering high

manipulation forces and its accurate bimanual control. There is only ex vivo data so far and it remains to be seen if these benefits can be replicated during in vivo trials.

6.4.3 Future Robotic Directions

6.4.3.1 Shared Autonomy and Artificial Intelligence

In 2017 Yang et al suggest a six level framework of autonomy in medical robots ranging from level 0 (no autonomy) to level 5 (full autonomy) (277). Surgical robots have in some cases reached level 3 (conditional autonomy: system generated tasks which the operator approves). However, in endoluminal surgery such as ESD the robotic systems still lie at level 0 with some of the above projects discussed demonstrating level 1 autonomy (robot assistance but human has continuous control).

Endoluminal surgery involves circumferential target dissection as one of its key steps. Ma et al proposed that this key step could be automated [ref]. They published their early work on a framework involving an operator defined trajectory and adaptive control of a flexible manipulator with three degrees of freedom. The system's dynamic response to material deformation and external payloads allowed ongoing accuracy during dissection. This demonstration shows the potential for shared autonomy in the control of instruments and the potential to automate a key step of ESD. (278)

Deep learning and more specifically convolutional neuronal networks have allowed significant advancement in image and video processing. This has resulted in many commercially available lesion detection and characterisation systems being recently released.

Utilisation of artificial intelligence beyond lesion detection and recognition in luminal endoscopy is hampered by the deformability of the gut. In order for intelligent navigation of the lumen by an endoscope both the highly malleable shape of the gut and the position of the camera must be estimated together, which remains a challenge to the engineering community(279). Although simple surgical tasks have been successfully automated through artificial intelligence, these as yet are not safely achievable on deformable tissue. This is a

rapidly evolving field and the continuing advancement of artificial intelligence driven endoluminal techniques should be expected both in navigation and therapeutics.

6.4.3.2 Soft Robotics

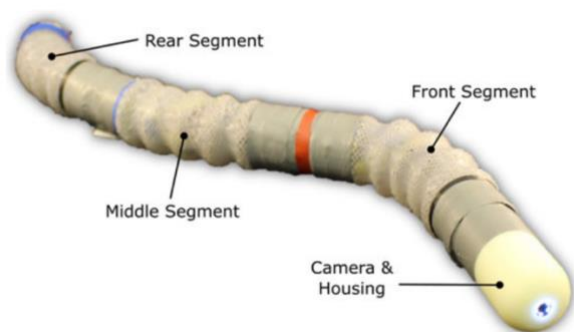


Figure 6.18 Meshworm

Soft robotics uses highly elastic material comparable to biologic tissues(280). Soft robots are able to adjust their stiffness. This would allow soft robots to navigate the lumen in a soft atraumatic configuration and stiffen at the point of intervention to allow stability during therapeutic intervention (244).

Common soft robotic actuators still have limitations preventing their use currently for therapeutic endoscopy. Shape memory actuators change shape on heating, but the heat required currently could cause damage to surrounding tissues. Dielectric elastomers deform with electric current but currently generate low and delayed forces (281).

Bernth et al. designed the 55cm silicone mesh, earthworm inspired, 'meshworm' soft robot (Figure 6.19) with a USB camera in the tip. Its three segments are actuated by antagonistic tendons driven by small pulley motors. In a prototyped plastic colon the meshworm averaged a speed of 1.21ms/s which equates to 30 minutes for an average caecal intubation (282).

STIFF-FLOP is a silicon based soft robot inspired by octopus tentacles. It is actuated by a combination of pneumatics and granular jamming. Granular jamming is where devices can take on liquid, solid or in between states producing variable stiffness (283). Pneumatic actuation

pressurizes three chambers in different combinations to produce a variety of movements (259). This combination allows navigation, elongation and stiffening. STIFF-FLOP has been successfully demonstrated in two cadaveric total mesorectal excisions acquiring superior visual angles of the surgical field (284).

Soft robotics offers exciting benefits including variable stiffness, minimised trauma and increase manoeuvrability with Magnetic Resonance Imaging compatibility for endoscope localisation but substantial technological progress is required before it can be incorporated into mainstream use.

6.5 Conclusion

The conventional endoscope control system has remained similar for over 50 years. This control system and the flexibility of the endoscope provides challenges to endoscope control and therapeutic endoscopy including motion hysteresis, compromised triangulation and resultant high endoscopic workload.

The therapeutic potential of the endoscope is being increasingly recognised and collaboration with engineers is helping to address the technical issues faced in fine instrument control and manipulation through a flexible device. This chapter presents novel robotic platforms allowing intuitive control of both the endoscope and endoscope instruments many of which have shown feasibility and increased intuitiveness in both simulated and real environments but remain predominantly in the research arena and not available for commercial use. Soft robotics and shared autonomy represent exciting potential directions.

The platforms presented show that intuitive control is possible but many of these systems require an entirely new and expensive system with a large footprint. Nonetheless the potential of a novel control system to enable safer and more accessible advanced therapeutic endoscopy is an exciting direction of endoscopy research travel.

7. Development of the Gaze Control System – Benchtop Trial

Content from this Chapter was Published in (285,286):

Sivananthan A et al. A novel gaze-controlled flexible robotized endoscope; preliminary trial and report. *Surg Endosc.* 2021;35(8):4890-4899. doi:10.1007/s00464-021-08556-1

Sivananthan A, et al. Gaze Controlled Endoscopy. *Surgical Life* 2021, 59: 28-31

Content from this chapter was Presented at:

Sivananthan, A et al. Eye Controlled Endoscopy – A Benchtop Trial of a Novel Robotic System. Poster Presentation. DDW 2023 Chicago

7.1 Background

The remit of luminal endoscopy is expanding, particularly with regards to third space endoscopy. Third space endoscopy technique requires micro precision of endoscopic control. Endoscopic submucosal dissection is a useful technique to allow endoscopists to remove lesions that would otherwise require surgical resection thus reducing the associated length of stay and surgical complications. Similarly in well selected cases ESD increases complete resection rates and recurrence versus endoscopic mucosal resection.

However, ESD has a higher complication rate, a steep learning curve and as such the technique is limited to a small number of highly experienced endoscopists. ESD is compromised by the challenges resultant of the flexible endoscope including hysteresis, a narrow field of triangulation and lack of device stability.

Novel robotic systems have been developed as discussed in chapter X but these are expensive, have a large footprint and still require bimanual control and in some case the use of two endoscopists(66,252,276,287,288).

A variety of tools have been developed to provide an ESD ‘toolbox’ as discussed in Chapter 5 but these only partially mitigate the issues faced by ESD practitioners(67).

To steer and reorientate an endoscope the endoscopist must take in the visual input of the monitor, translate that into the 2 degrees of freedom in the knob steering system of the endoscope with additional movements provided by two degrees of freedom in torquing the endoscope and insertion/ withdrawal of it. The cognitive burden of this visual attention is a key component as demonstrated by the value addition of CADe systems as shown in Chapter 3 (289). Similarly disorientation within the lumen is common during flexible endoscopy as demonstrated in Chapter 4 (87). Overall, this suggests that endoscopic control during luminal endoscopy places a high burden on visual attention as shown by the common missing of lesions and disorientation.

We theorise that an endoscopic system that steers following the natural gaze of an endoscopist may be an intuitive device. Using the natural visual movements of an endoscopist frees up the endoscopist hands resulting in lower cognitive workload with intuitive hands-free reorientation of the endoscopic view.

A large barrier to the wide uptake of robotic therapeutic endoscopy systems is the requirement for an expensive large system with a large footprint.

Aims of this experiment:

1. Motorise and robotise an existing endoscope in a cheap and replicable way
2. Develop a gaze control system to steer the endoscope
3. Assess the feasibility of such a system
4. Compare the experience of system use versus conventional endoscopy

7.2 Development of Gaze Control System

7.2.1 Robotisation of the Endoscope Steering Knobs (290)

Standard endoscopes have 2 degrees of freedom of control via the two steering knobs. The steering knobs control the bending tip of the endoscope, done via Bowden cables. Rotation of the knob turn the angulation wires, with the resultant tension causing bending with the bending section of the tip (Figure 7.1) (211).

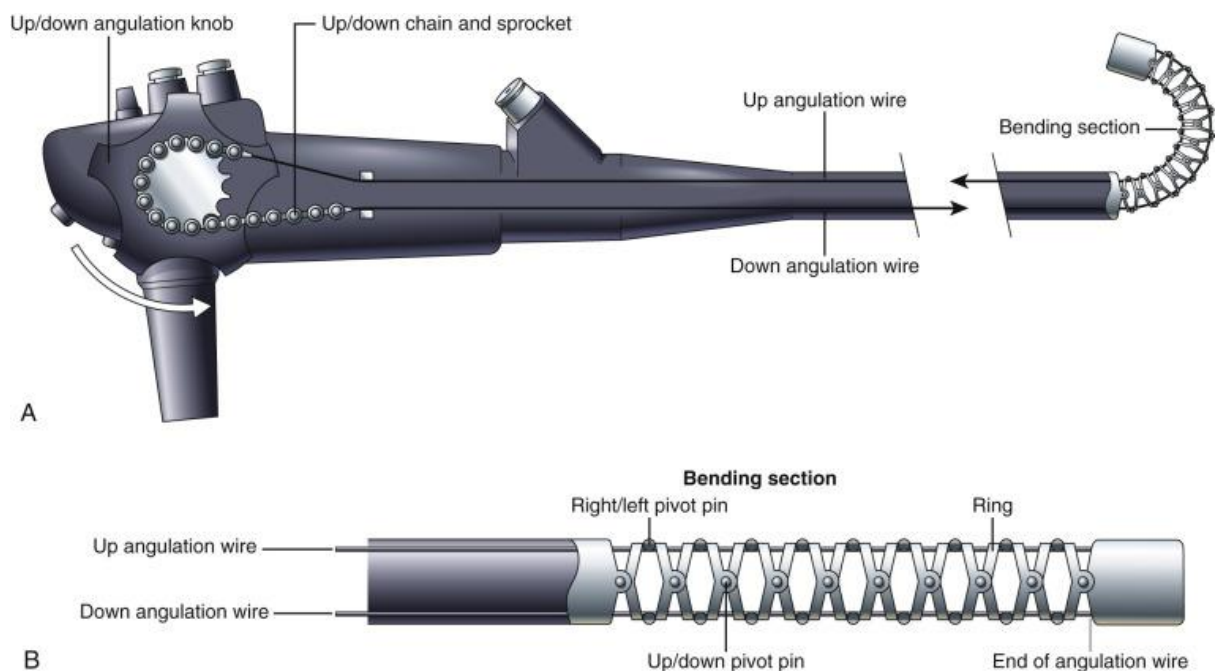


Figure 7.1 Anatomy of endoscope steering with angulation wires

The larger steering knob rotates the tip up and down. The smaller steering knob rotates the tip left and right.

3D gears were developed in Solidworks and printed by an Ultimaker 2+ printer. Gears were printed for the steering knobs and placed over each one. The gears were actuated by two DYNAMIXEL RX-24F motors (Figure 7.2) (291).



[RX-24F]

Figure 7.2 Dyanmixel Motor (Robotis Techsupport)

Matching gears were similarly printed to attach to the motors and these gears directly controlled each steering knob with a motor on either side.

A USB2 DYNAMIXEL motor driver took inputs from the computer via USB and outputted them via the Dyanmixel motors (Figure 7.3) (291)).

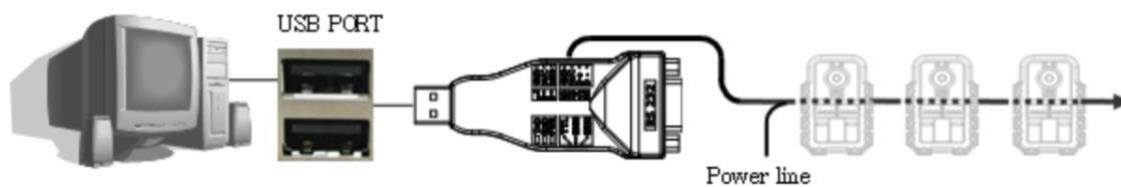


Figure 7.3 USB DYNAMIXEL motor driver, driving 3 motors connected in series from computer

7.2.2 Robotisation of Endoscope Torque and insertion.

A further degree of freedom is provided during endoscopy through torque rotation. This involves the endoscopist rotating the shaft clockwise or anticlockwise with the right hand. The final degree of freedom in conventional endoscopy is provided by insertion and withdrawal of the endoscope.

The endoscope was mounted on a robotic arm (Universal Robotics UR5) allowing rotation and insertion/ withdrawal of the endoscope (Figure 7.4). The shaft of the scope was aligned to a guiderail for additional support of the flexible endoscope allowing no use of the hands.

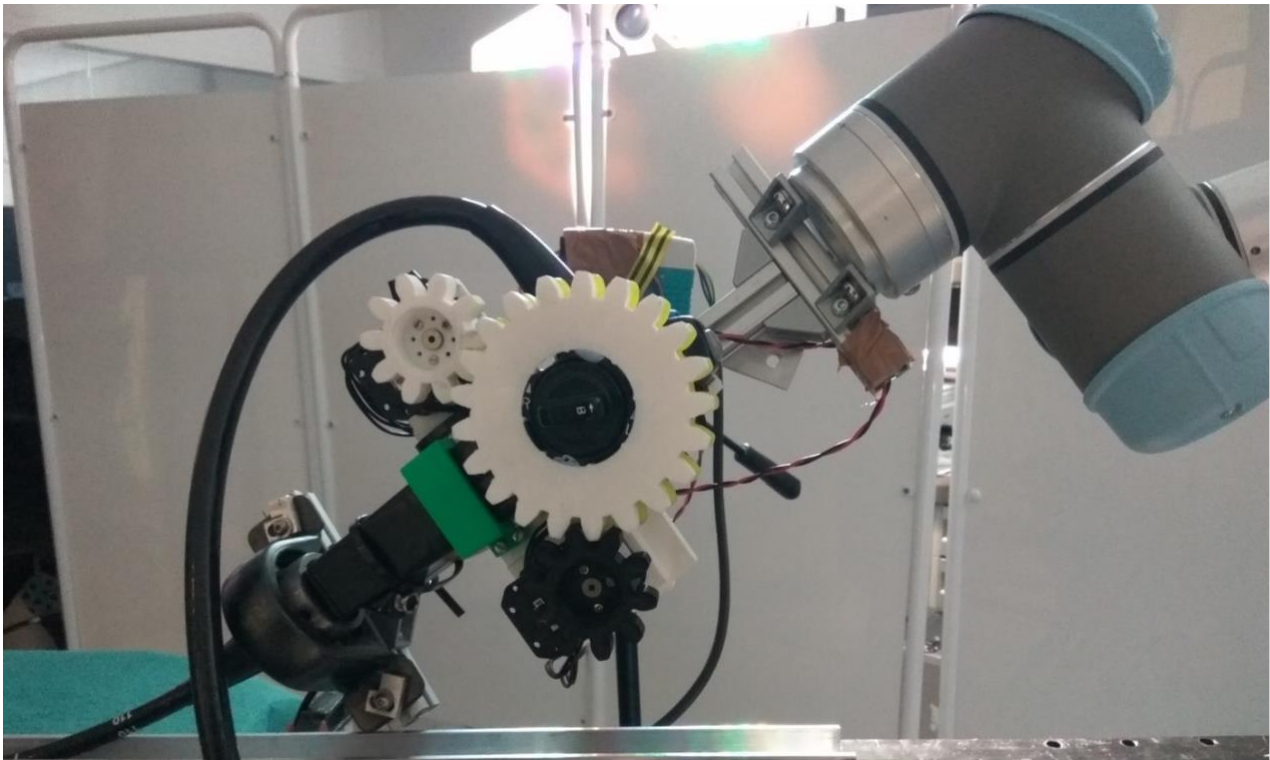


Figure 7.4 Motorised System showing Universal Robotics UR5 arm and motorised printed gears

7.2.3 Torque and Speed Settings of Motor

Work previously done by Reilink et al. were used to inform safe setup of the motors as regards torque and speed. For rotation of the large knob a torque of 0.4N/M is required and a speed of 15 revolutions per minute.

7.2.4 Eye Position and tracking

Eye tracking was captured using eye tracking glasses (SMI - SensoMotoric Instruments GmbH). These glasses can track the movements of both pupils in real time at a high capture rate of 120Hz.

Head position was captured using an OptiTrack Motion Capture System. Six small spheres were attached to the eye tracking glasses which allow the Optitrack to estimate the head position by detecting the position of the eye tracking glasses in space .

7.2.5 Eye Tracking in Steering

The control point - $y(t)$, is the centre of the screen. The eye tracking glasses recognise a fixation point which is taken as the reference point $r(t)$. The difference between the reference point (where the user is looking – fixation point) and the control point gives the error $e(t)$ (Figure 7.5).

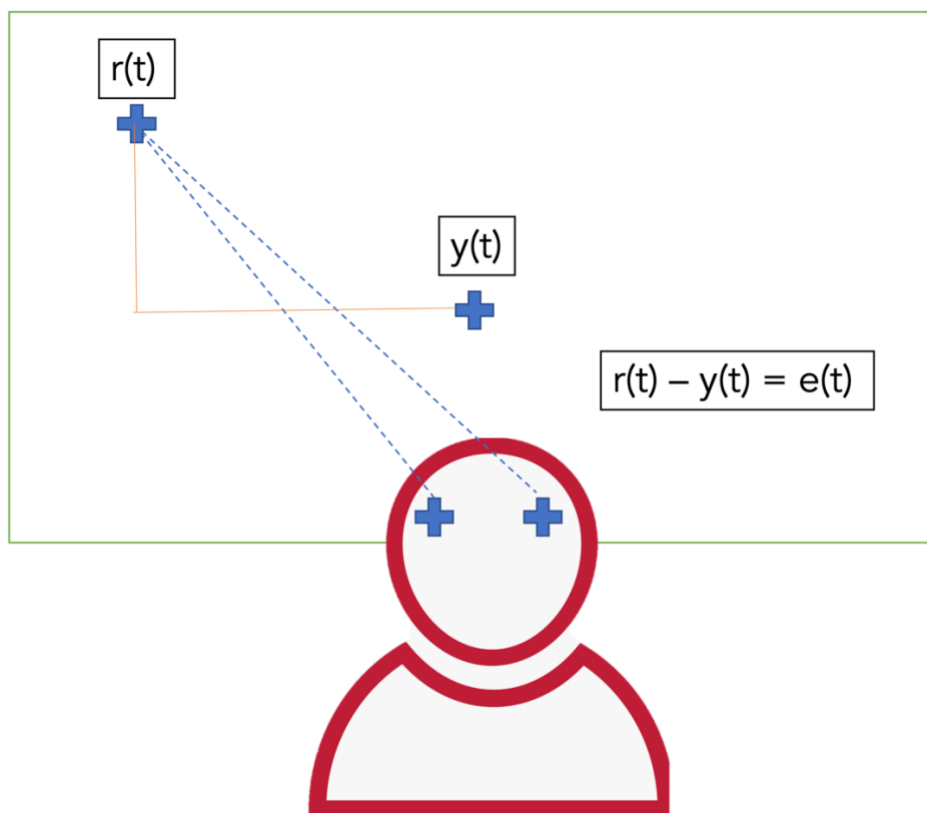


Figure 7.5 Gaze Steering: $r(t)$ = reference point, $y(t)$ = control/ centre of monitor, $e(t)$ = error signal

The error value is inputted into the PID (proportional integrative derivative controller). The error signal provides relative x and y co-ordinates. The x-co-ordinate inputs to control of the small steering knob to move left and right and the y co-ordinate inputs to control the large steering knob to move up and down. The PID controller via the computer will calculate the desired velocity of both Dyanmixel motors to produce this.

After this gaze ‘fixation’ input and output via the motors to steer the endoscope the reference point should move to the centre reducing the error $-e(t)$ to 0 as the centre and fixation point are now the same thus closing the loop. If these do not match the loop will restart until the point of gaze matches the centre of the screen (Figure 7.6).

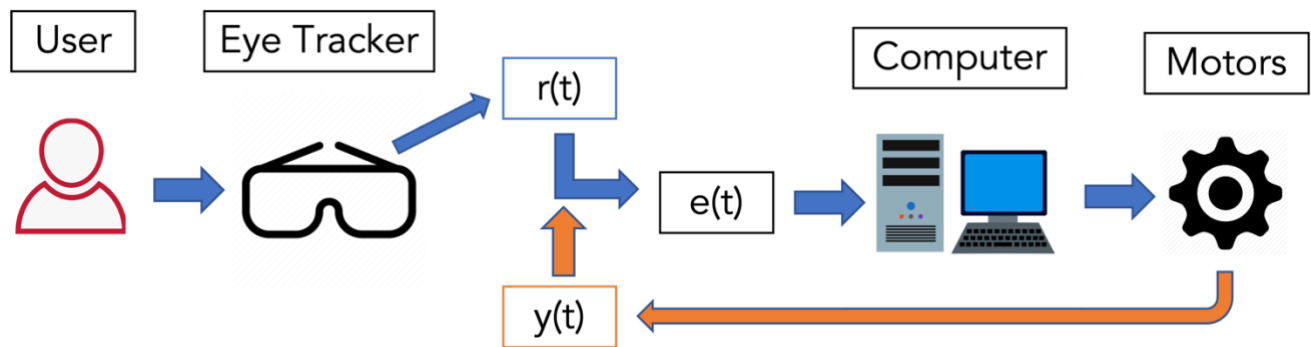


Figure 7.6 Closed Loop Logic

User's gaze generates reference point $r(t)$, the difference between this and reference point $y(t)$ produces error signal $e(t)$ which is passed to controller to generate appropriate velocity to steering motors which should allow $y(t)$ to equal $r(t)$ otherwise the loop begins again.

7.2.6 Eye Tracking and Rotation

Rotation or torque of the endoscope follows a similar algorithm to tip steering. The control point here however is a horizontal line: $y(t)$. The reference point $r(t)$ is taken as a line between the x/y co-ordinated of the left and right eye (Figure 7.7). The relative difference between the head tilt ($r(t)$) and the horizontal plane ($y(t)$) gives the error $e(t)$ (Figure 7.8). The PID calculates the required motor velocity to the dynamixel motor to provide rotation of the endoscope shaft. Matching of the reference plane and the control plane will close the loop (295).

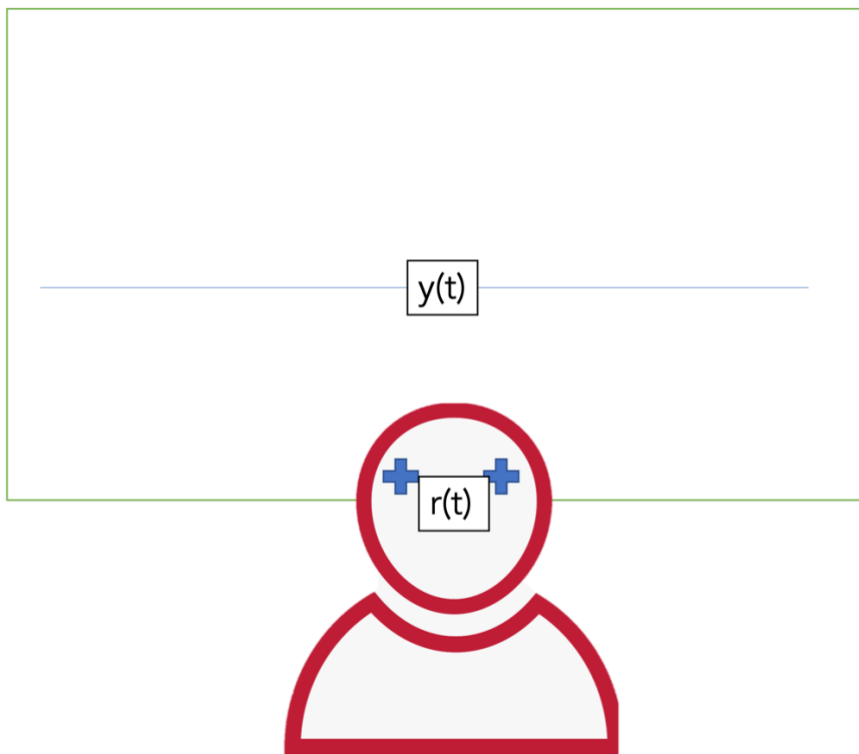


Figure 7.7 Gaze Rotation in neutral Position: $r(t)$ = reference point, $y(t)$ = horizontal control

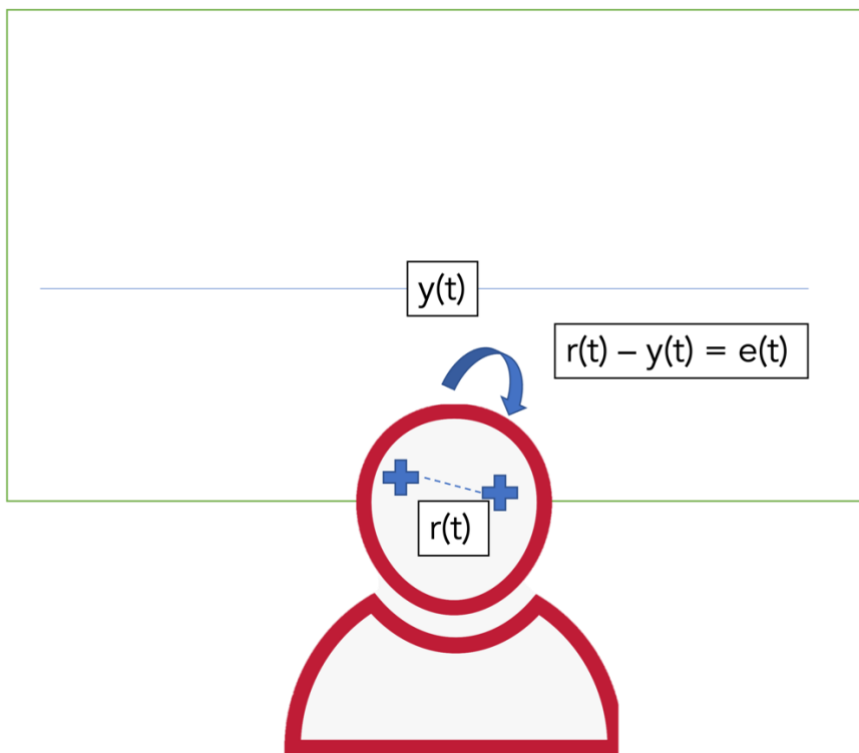


Figure 7.8 Gaze Rotation

The difference between reference point $r(t)$ and control $y(t)$ gives the error $e(t)$ as the rotational difference needed.

7.2.7 Recognising Eye Movements

Saccadic eye movements are rapid movements of both eyes. Saccadic movements happen in the background of human vision to help rapid scanning to build up a three dimensional 'map' of the scene. In saccadic eye movements the eyes move as quickly as the eyes are able.

Smooth pursuit eye movements are intentional voluntary smooth movements of both eyes to a point of fixation. Fixations are maintenance of gaze in a fixed location.

The gaze system needs to recognise 'fixations' to appropriately move the eye gaze control system to the intended area of the operator. When interpreting the gaze pattern inputs to ensure only meaningful fixations are recognised and saccadic movements are filtered out the following eye movements were filtered out:

- 'dwell' times of less than 0.2 seconds– i.e., directional gaze was only noted by the system if fixation was greater than 0.2 seconds.
- 'High velocity' eye movements of greater than 36 degrees angle change per second

7.2.8 Monitor and Computer Based Systems

Endoscopic views were displayed on a high-definition LG monitor (42 inch with 1920X1080 pixels). A PC running Windows 10 ran the eye gaze and motion capture modules with Ubuntu 14.04 for all other modules.

7.2.9 Safety Measures

Each operator completed a nine-point calibration step before use of the system. This comprised the user looking at set fixed points in sequence from the position in which they would use the system.

As a further safety measure, any gaze directed outside the endoscopy monitor would pause the robotic system as well.

In addition, a further optional control system was provided by use of a two-axis joystick controller. A button on this controller allowed for retroflexion of the endoscope and pressing any other button paused the system. The joystick could be moved in and out to allow for insertion and withdrawal of the endoscope.

The two-axis joystick was connected to the system via an Arduino One Microcontroller.

7.2.10 User Interface

The operator sat in front of the screen in an ergonomically neutral posture whilst 2 meters away from the screen. Eye tracking glasses were worn by the user. The joystick was also held by the user as required (Figure 7.9).

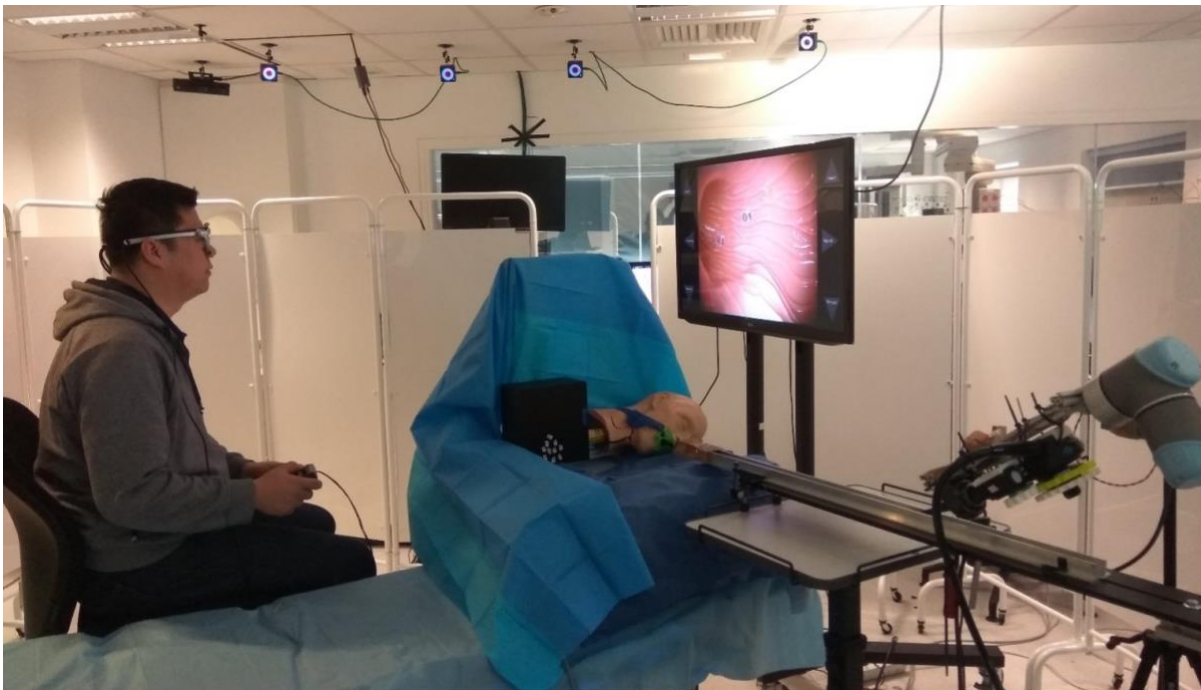


Figure 7.9 Setup of System and Benchtop Trial with Task 2

As previously described tip steering was actuated by the operators gaze fixations as relative to the centre of the display (Figure 7.10). Rotation of the endoscope was actuated by head tilt beyond ± 20 degrees as relative to the horizontal plane of the display. This mimicked endoscopists' instinct to rotate their head in reorientation of the endoscope.

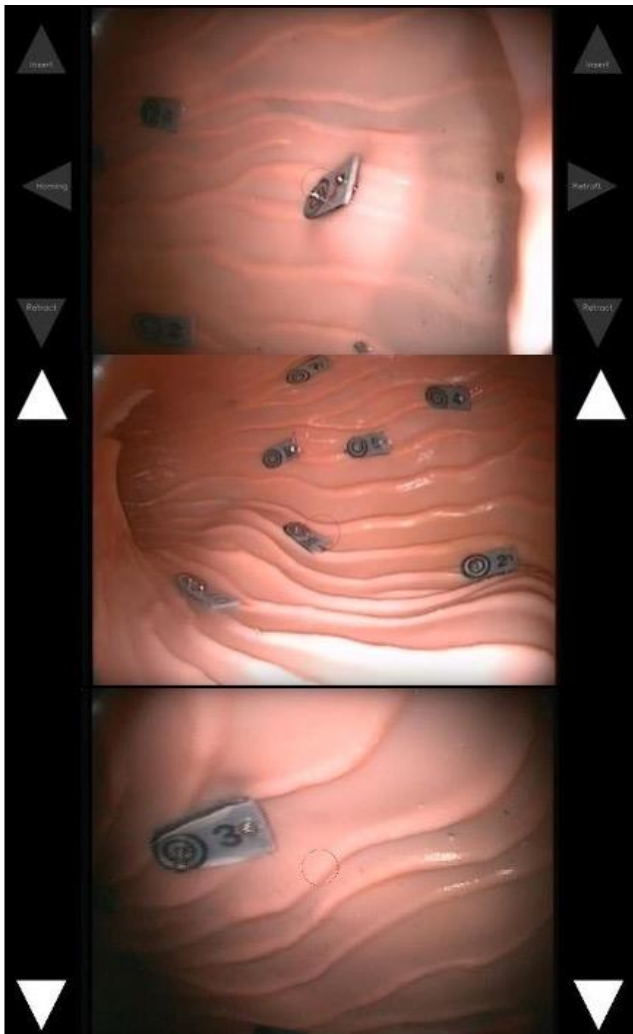


Figure 7.10 Monitor display with corresponding arrow showing direction of steering.

Audible alerts were inbuilt to give the operator clear feedback. When the system-initiated rotation, an audible alert was issued saying “left” or “right”. When the head tilt levelled to within the permissible range (i.e. the co-ordinates of the left and right eye were within ± 20 degree of the horizontal plane) the endoscope rotation ceased with a further audible alert saying “straight”.

Insertion and withdrawal were controlled by moving the joystick up or down with corresponding audible alerts saying “in” or “out”. Retroflexion was initiated Retroflexion, on the other hand, was initiated by holding the joystick controller to the right for a duration of one second or longer, accompanied by an audible alert stating "retroflexion." Pressing a button on the joystick paused the movement of the endoscope, resulting in an audible alert saying "pause," and it remained in that position until the button was pressed again, producing an audible alert saying "unpause."

7.3 Benchtop Trial Study Design

The study was setup as a benchtop feasibility study to trial the system in a simulated environment. The gaze control system was compared to a conventionally controlled endoscope.

Eight experienced endoscopists and eight non endoscopist participated. All participants provided written consent for utilisation of all data.

Experience endoscopists were defined as those certified as independent by the UK Joint Advisory Group Endoscopy Training System. For certification 300 observed OGDs and 20 examined OGDs are required. In addition, attendance at a mandatory course is required. The age range of the endoscopist group was between 32 and 51years.

Non-endoscopists were defined as those who had no experience in any form of gastrointestinal endoscopy. This group was made up of seven non-clinical scientists and one ENT surgeon. The age range of the non-endoscopist group was between 24 and 42years.

None of the participants had any experience using or designing the robotic system.

All participants followed a standardised familiarisation process for both the eye gaze and conventional endoscope using written instructions, a facilitator, and a set period of time. They were given a flat sheet with targets to practice use of the systems on.

They then used both systems in two simulated environments to identify ten targets in each. The first simulated environment was a sphere and the second was an upper gastrointestinal (UGI) model. Tasks were completed to assess the efficiency, ergonomics, and stability of the device.

7.3.1 Task 1

The simulated environment was a 20cm diameter plastic spherical cavity with an 11mm circular entry port. The tip was inserted 1cm inside and this was the start point for the target. Ten numbered targets were distributed around the internal wall of the sphere to require different positions and orientation (Figure 7.11).

A circle of 400-pixel diameter was placed at centre of the monitor. The participant then identified each target in sequence by placing the numbered target within the circle with the endoscopic field of view showing the 'upright' position. The tenth target was placed so it required retroflexion of the endoscope to successfully identify it.

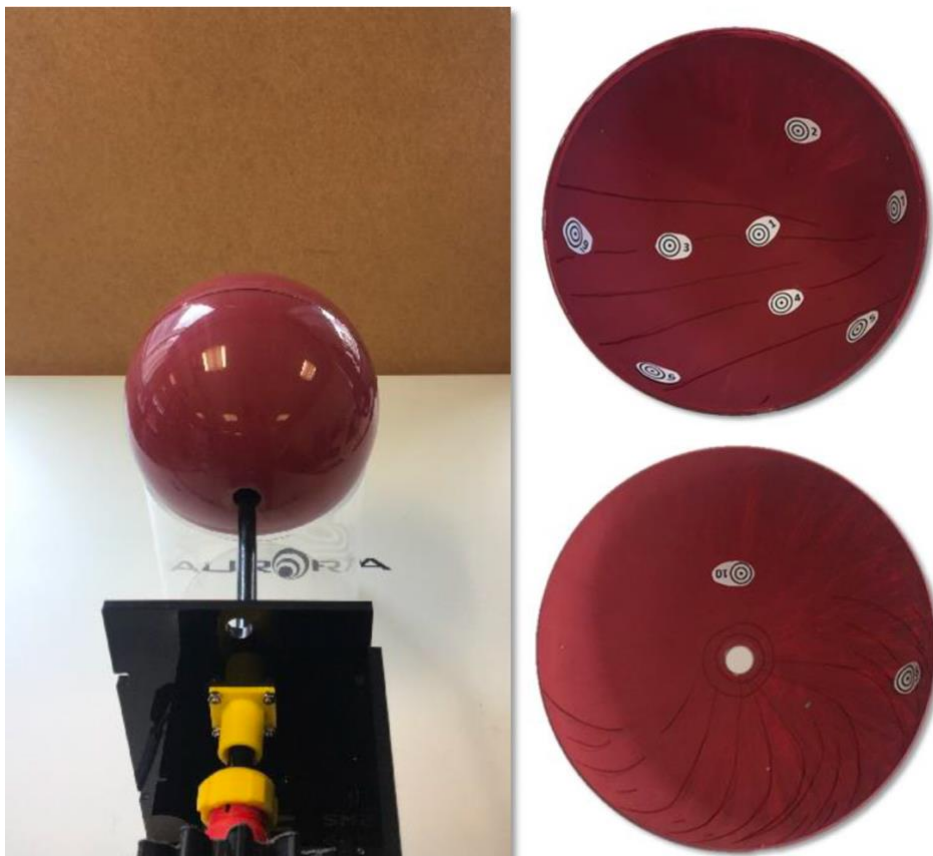


Figure 7.11 Setup of Task 1 with enclosed spherical phantom (left), internal views (right)

7.3.2 Task 2

The simulated environment was an anatomical model of the upper GI tract ((The Chamberlain Group, MA, USA). starting from the mouth down to the second part of the duodenum. The starting point was at the level of the incisors. Ten numbered targets were placed in the inside of the stomach. The participant was required to intubate the oesophagus by passage through the mouth, past the pharynx, through the oesophagus and into the stomach via the gastro-oesophageal junction. As above the participants were required to place each numbered target within the central circle in the upright position (Figure 7.12).

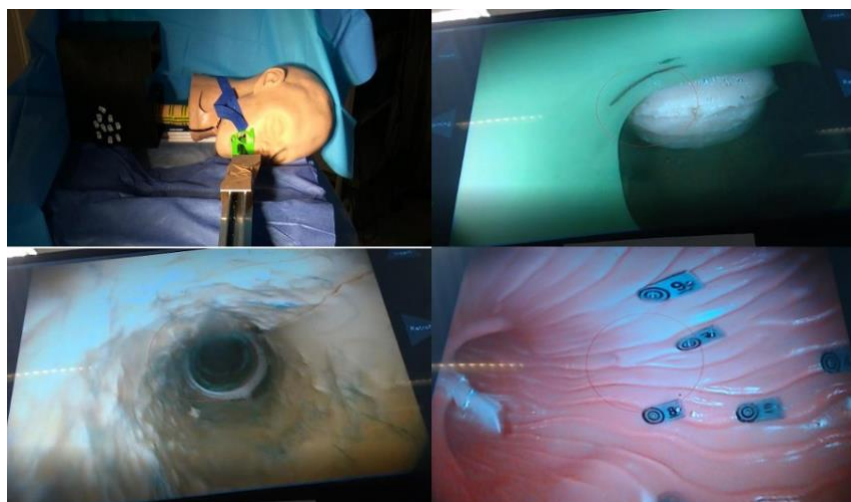


Figure 7.12 Setup of Task 2 with head model top left, oropharynx top right, oesophagus bottom left and stomach bottom right.

7.3.3 Order of Tasks

Each participant was randomised to which system they would use first: the conventional endoscope and gaze control system. Participants then underwent the standardised familiarisation protocol. After completion of one control method on both targets with one system they then underwent the familiarisation protocol for the other system and the completed the tasks again. Task 1 was always done first followed by Task 2. Feedback was collected after the use of each method to avoid recall bias.

Outcomes:

- *Objective outcome measures*

The total time to complete each task was recorded to the nearest second.

- *Subjective Feedback*

Subjective feedback was directly collected after the tasks were completed. Participants answered questions to assess their task load, acceptance of the technology and ergonomic design.

7.3.4 Task Load

The NASA-TLX (Task Load Index)(296) was used to assess task load (Figure 7.13). This is a multi-dimensional ten-point visual analogue scale to subjectively assess cognitive workload. Use of this score has been validated in studies of both diagnostic and therapeutic endoscopy (297–300)

NASA-TLX questions	
Mental Demand	How much mental and perceptual activity was required? Was the task easy or demanding, simple or complex?
Physical Demand	How much physical activity was required? Was the task easy or demanding, slack or strenuous?
Temporal Demand	How much time pressure did you feel due to the pace at which the tasks or task elements occurred? Was the pace slow or rapid?
Own Performance	How successful were you in performing the task? How satisfied were you with your performance?
Frustration	How irritated, stressed, and annoyed versus content, relaxed, and complacent did you feel during the task?
Effort	How hard did you have to work (mentally and physically) to accomplish your level of performance?

Figure 7.13 NASA-TLX questions

7.3.5 Acceptance of New Technology

The Van der Laan acceptance scale(301) is a five point scale including questions on perceptions of usefulness and satisfaction with the technology. The five-point scale ranges from -2 to +2.

7.3.6 Ergonomics

A standardised questionnaire was completed by all participants to assess the usability and ergonomics of the system. This consisted of a seven-point Likert scale (Figure 6.14).

My Judgement of the (...) system are ... (please tick a box on every line)			
1	useful	☐ ☐ ☐ ☐ ☐	useless
2	pleasant	☐ ☐ ☐ ☐ ☐	unpleasant
3	bad	☐ ☐ ☐ ☐ ☐	good
4	nice	☐ ☐ ☐ ☐ ☐	annoying
5	<u>effective</u>	☐ ☐ ☐ ☐ ☐	superfluous
6	irritating	☐ ☐ ☐ ☐ ☐	irritable
7	assisting	☐ ☐ ☐ ☐ ☐	worthless
8	undesirable	☐ ☐ ☐ ☐ ☐	<u>desirable</u>
9	raising alertness	☐ ☐ ☐ ☐ ☐	sleep-inducing

Figure 7.14 Ergonomics Questionnaire

7.3.7 Data Analysis

The reported timings of tasks were presented as mean values along with their standard deviations. NASA-TLX scores were reported as means rounded to one decimal place, while Van der Laan's scores were reported as means rounded to two decimal places.

The comparisons made in the following sections were conducted using within-subjects analysis in the following cases:

- Comparing task completion time between endoscopists using conventional endoscopy versus gaze-controlled endoscopy.
- Comparing task completion time between novices using conventional endoscopy versus gaze-controlled endoscopy.
- Comparing NASA-TLX scores between endoscopists using conventional endoscopy versus gaze-controlled endoscopy.

- Comparing NASA-TLX scores between novices using conventional endoscopy versus gaze-controlled endoscopy.

Between-subjects analysis was performed in the following scenarios:

- Comparing task completion time with conventional endoscopy between endoscopists and novices.
- Comparing task completion time with gaze-controlled endoscopy between endoscopists and novices.
- Comparing NASA-TLX scores with conventional endoscopy between endoscopists and novices.
- Comparing NASA-TLX scores with gaze-controlled endoscopy between endoscopists and novices.
- Comparing Van der Laan's scores between endoscopists and novices.
- Comparing ergonomics assessment scores between endoscopists and novices.

For within-subjects analysis, the normality of the paired differences was assessed using the Shapiro-Wilk test. If the test was successful and no outliers were detected, a paired-samples t-test was conducted. In cases where the differences were not normally distributed or outliers were present, the Wilcoxon signed-rank test was used.

For between-subjects analysis, the normality of the samples was assessed using the Shapiro-Wilk test. If the test was successful, an independent-samples t-test was performed. If any of the two samples did not follow a normal distribution, the Mann-Whitney U test was applied.

A significance level of $p < 0.05$ was used for all statistical tests. The statistical analysis was performed using SPSS version 25.

7.4 Results

7.4.1 Performance Between Groups

All tasks had a 100% completion rate by all participants.

When using the conventional endoscope the experienced endoscopists were significantly quicker in completing both task 1 ($1:24 \pm 0:39$ vs $9:05 \pm 5:40$ minutes, $p=0.006$) and task 2 ($1:27 \pm 0:20$ vs $3:45 \pm 0:53$ minutes, $p<.001$).

When using the gaze control system there was no significant difference between task performance.

7.4.2 Performance Within Groups

Expert endoscopists were significantly quicker using the conventional endoscope versus gaze control in both task 1 ($:24 \pm 0:39$ vs $3:18 \pm 1:14$ minutes, $p=0.002$) and task 2 ($:27 \pm 0:20$ vs $2:10 \pm 0:35$ minutes, $p=0.006$)

Non expert endoscopists were significantly quicker when using the gaze control system in both Task 1 ($3:54 \pm 1:17$ vs $9:05 \pm 5:40$ minutes, $p=0.012$) and Task 2 ($:59 \pm 0:24$ vs $3:45 \pm 0:53$ minutes, $p<.001$) (Table 7.1 and Figure 7.16).

		SPHt	UGIt	NASA-TLX
Endoscopists	Gaze Control	3:18 ($\pm 1:14$)	2:10 ($\pm 0:35$)	54.2 (± 16)
	Endoscope	1:24 ($\pm 0:39$)	1:27 ($\pm 0:20$)	26.9 (± 15.3)
Non Endoscopists	Gaze Control	3:54 ($\pm 1:17$)	1:59 ($\pm 0:24$)	22.5 (± 13.8)
	Endoscope	9:05 ($\pm 5:40$)	3:45 ($\pm 0:53$)	80.6 (± 11.3)

Table 7.1 Time taken to complete tasks with each system by both groups

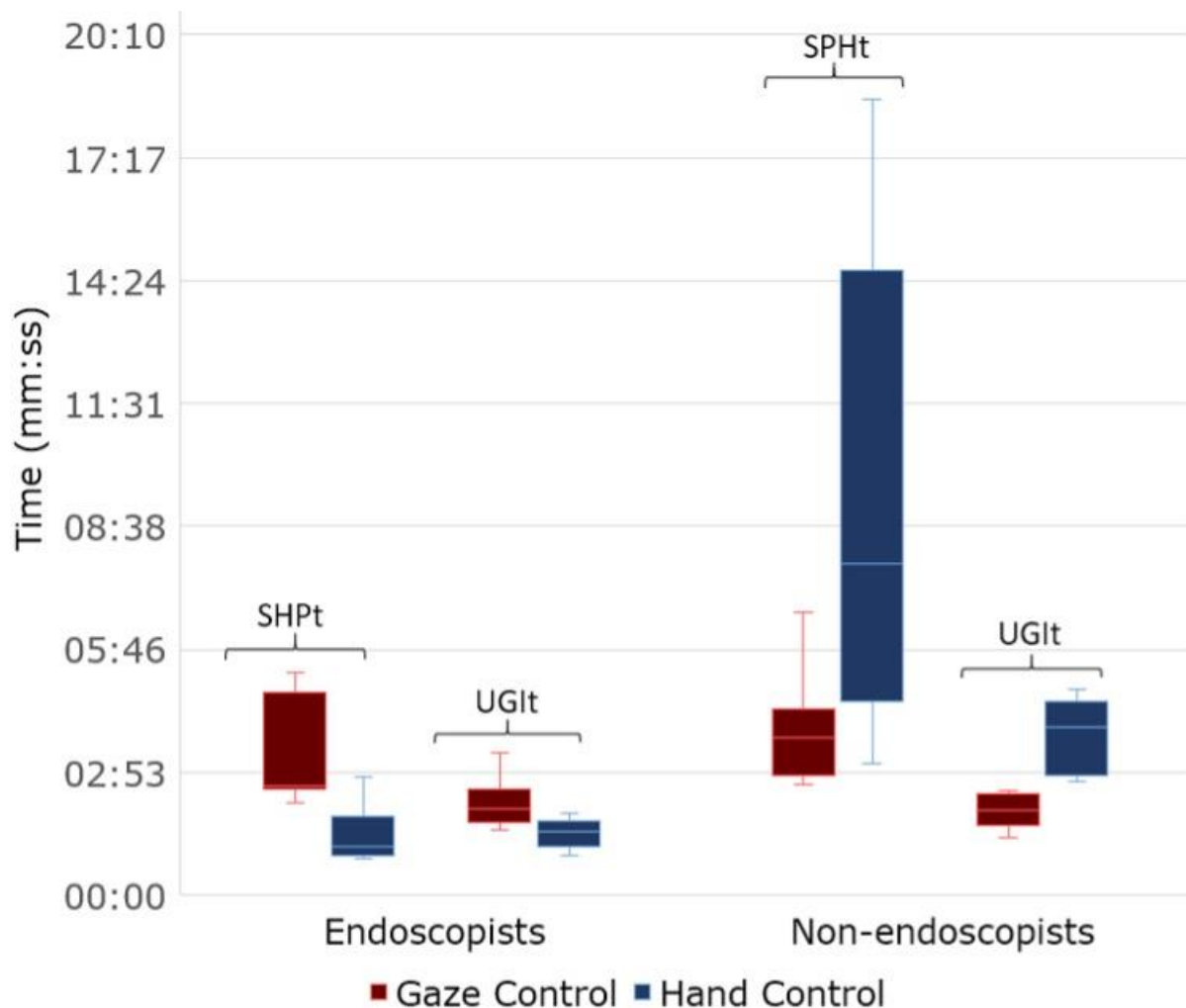


Figure 7.15 Graph showing Time Taken to Complete each Task by Both Groups

(SHPt = Sphere Task/ Task 1, UGI = Upper GI Task/ Task2)

7.4.3 Workload

Endoscopist experienced a significantly higher workload when using the gaze control system versus the conventional endoscope ((54.2±16 vs 26.9±15.3, $p=0.012$). There were significant differences in the 'effort', 'mental demand', 'temporal demand' and 'performance'.

Non endoscopists reported a significantly higher workload when using the conventional endoscope versus the gaze control system (80.6±11.3 vs 22.5±13.8, $p<.001$). There was a significant difference in all six workload domains; 'effort', 'mental demand', 'temporal demand' and 'performance', 'frustration' and 'physical demand' (Figure 7.16).

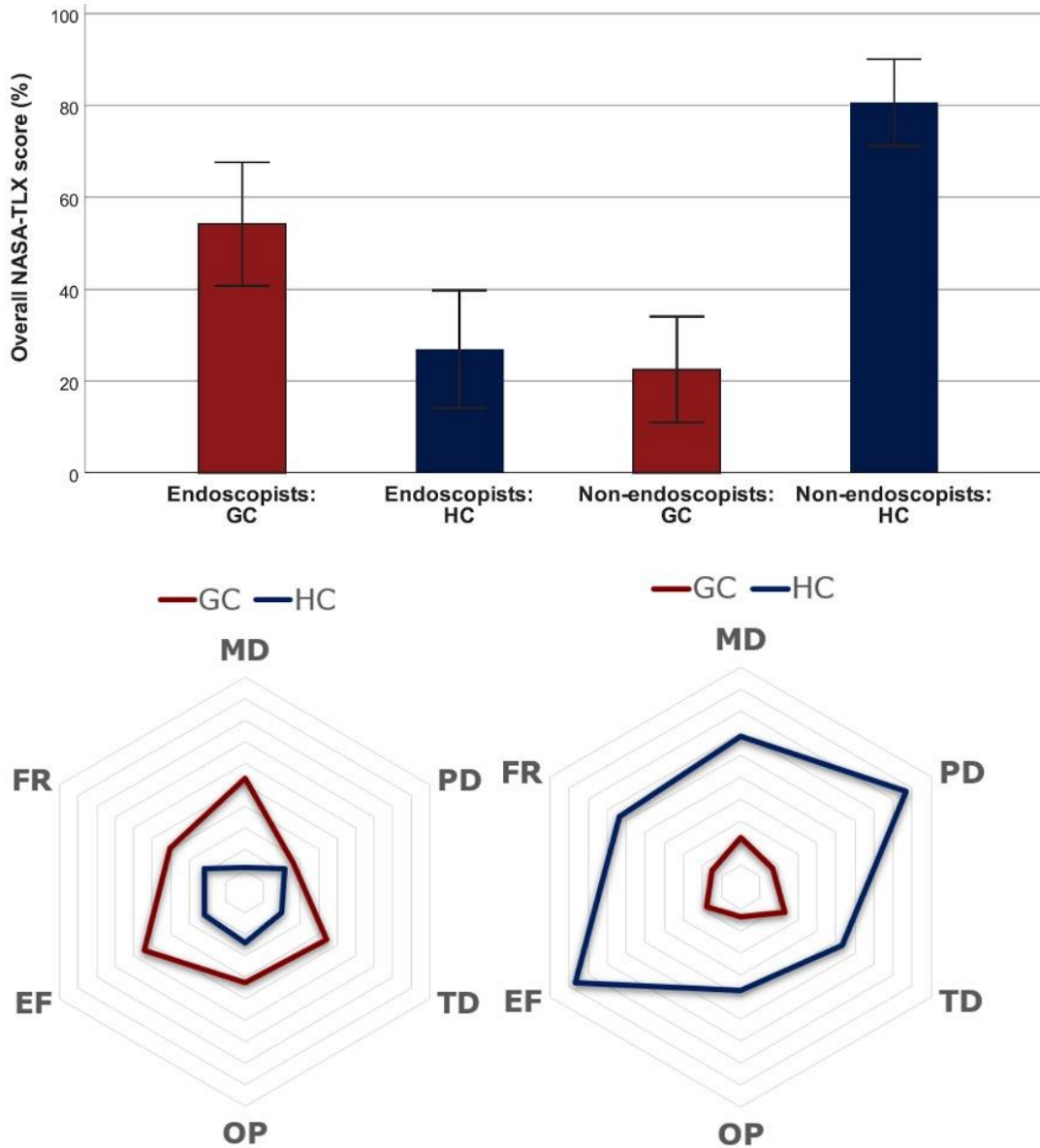


Figure 7.16 Top - NASA TLX score for Gaze Control (GC) and Hand Control (HC). Bottom - NASA TLX scores as a percentage extending out, by domain (clockwise)

MD- Mental Demand, PD – Physical Demand, TD – Temporal Demand, OP - Performance, EF – Effort, FR - Frustration

7.4.5 Technology Acceptance

All participants reported a positive usefulness score with the experienced endoscopists scoring it 0.56 ± 0.83 and the non-endoscopists scoring it 1.43 ± 0.51 .

All participants reported positive ‘satisfaction’ scores with the experienced endoscopists giving a score of 0.8 ± 0.87 and the non-experienced endoscopists scoring it 1.44 ± 0.68 (Figure 7.17).

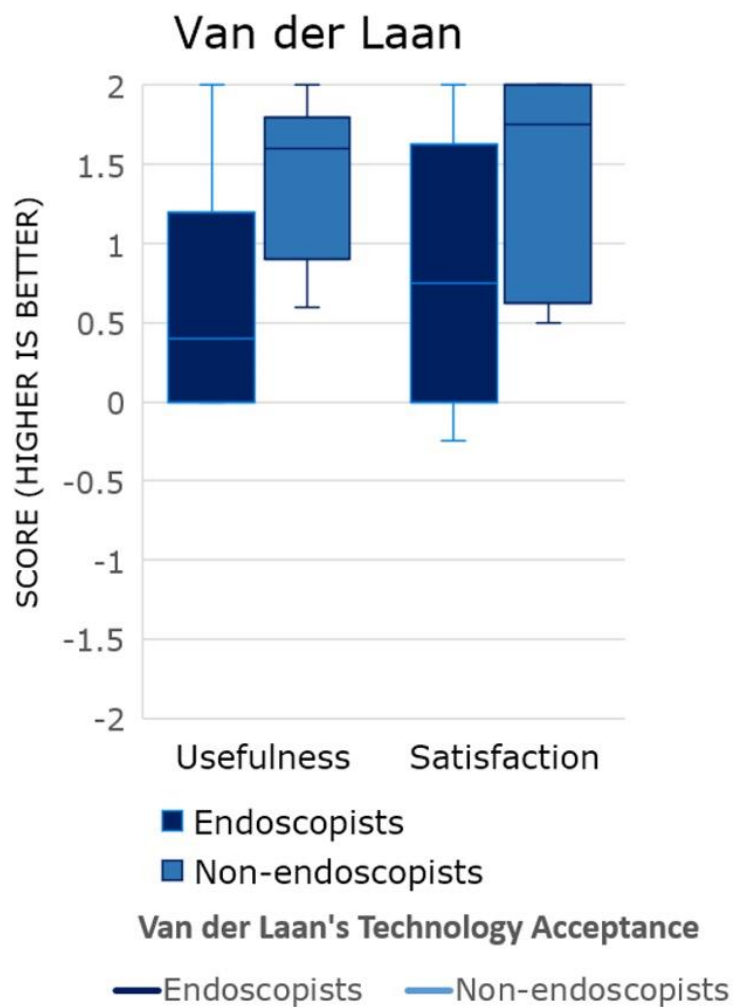


Figure 7.17 Top Van Der Laan acceptance Scores. Bottom – Van Der Laan Acceptance Score by Domain with higher scores at a greater radius.

7.4.6 Ergonomics

Experienced endoscopists reports poor ergonomics in all domains when using gaze control. Experienced endoscopist found eye gaze less comfortable (86%), more stressful (57%), interrupting of task flow (85%), uncomfortable for the neck (57%) strenuous for the eyes (86%) and fatigue causing (71%).

Non endoscopists reported gaze control to have good ergonomics across all the domains saying it was more comfortable (100%), easier to learn (100%), less stressful (100%), not task flow interrupting (100%), not uncomfortable for the neck (75%) not strenuous for eyes (51%) and not causing fatigue (88%) (Figure 7.18).

Statistical analysis confirmed significant differences between endoscopists and novices in comfort, ease of learning, stress, and task flow interruptions.

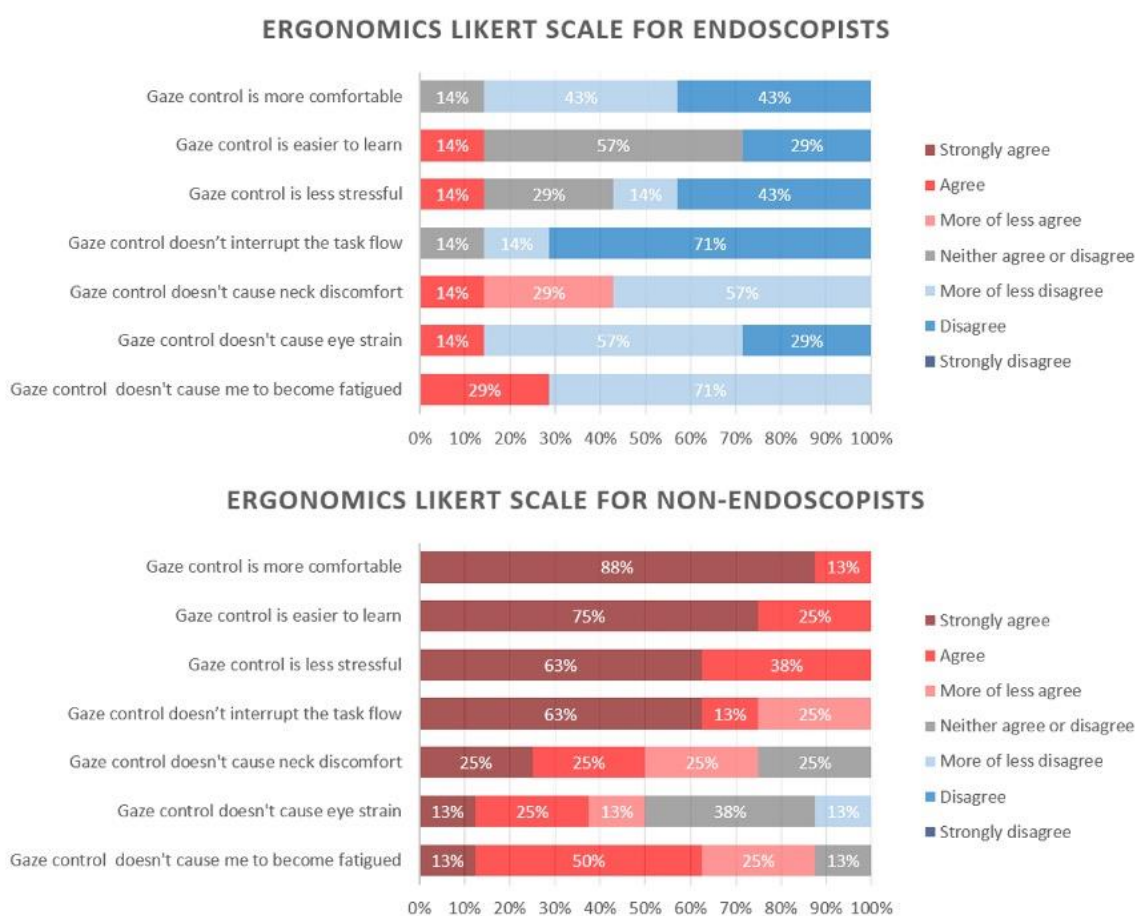


Figure 7.18 Top - Ergonomic Scores as a percentage of respondents for endoscopists for gaze control. Bottom- Ergonomic Scores as a percentage of respondents for non-endoscopists for gaze control.

7.5 Discussion

I have presented the feasibility data from a gaze controlled robotised flexible endoscope. This study showed the feasibility of this system to navigate through a simulated UGI lumen whilst maintaining fine motor control.

Experienced endoscopist are extremely familiar with conventional endoscope control and the fact they were faster completing tasks with the conventional endoscope likely reflects a familiarity with the control systems rather than the technical superiority of the control system of a conventional endoscope.

The non-endoscopists had no prior experience with either system and they interestingly performed quicker with the gaze control system. This may suggest the gaze-controlled system has a more shallow learning curve and is a more intuitive system compared to the convention endoscope control.

All reported that they were satisfied when using the gaze control system and that it was an acceptable technology.

Similarly, the ergonomic preference of the non-endoscopists to the gaze control system may suggest that the gaze control system is more ergonomically beneficial.

7.5.1 Limitations

The system used a Karl-Storz gastroscope and although it has the same control system as all conventional endoscopes it could be argued findings could not be applicable to other systems. Of note the simple gear printing and closed loop system would ensure the system could be quickly adapted to any endoscope. The close loop would account for any changes in different endoscope cable stiffness between scope models and with aging of endoscopes.

The trial occurred in a rigid environment which doesn't reflect the flexible and deformable tissue of the real-life gastrointestinal lumen. Our research team does have experience in motion compensation and depth extraction which could be a further point of development .

There is no tactile feedback for the gaze control system which is present in a conventional endoscope. Force feedback sensors could be attached to the endoscope shaft and motors and feedback either visually or through haptic feedback in future models.

The setup of the gaze control system currently, particularly with regards to the mounted rail take up a large footprint which may not be clinically practicable in the endoscopy suite.

This study only compared non-endoscopists to experienced endoscopists. To truly establish the learning curve and intuitiveness of the gaze control system versus the conventional endoscope a dedicated experiment with non-experienced endoscopists and repetition of task performance is required.

7.6 Conclusion

The use of a gaze control system to operate a fully robotised flexible endoscope is feasible. Non-endoscopists found the gaze control system had a lower workload and was more ergonomically favourable than conventional endoscopy and performed significantly better with the gaze control system.

Experienced endoscopists found conventional endoscopy had a lower workload than the gaze control system and performed better with the conventional endoscope which is likely reflected with significant experience with the conventional endoscope system(225).

Further study is required to truly evaluate the intuitiveness of the gaze control system versus conventional endoscopy.

8. iGAZE2

Content from this Chapter was Published in:

Sivananthan A et al. Eye-controlled endoscopy - a benchtop trial of a novel robotic steering platform - iGAZE2. *J Robot Surg.* 2024;18(1):266. Published 2024 Jun 25. doi:10.1007/s11701-024-02022-5

8.1 Background

In the previous chapters a novel gaze-controlled endoscope robotic system that can be retrofitted to any endoscope to allow gaze-controlled endoscope tip steering has been presented. Initial benchtop trials demonstrated the technologies feasibility(286). Using eye tracking glasses and a motorised system the endoscope tip follows the direction of the endoscopist's gaze. In the previous system head tilting, and forward and backward movement by the user was able to rotate and insert and withdraw the scope. The initial gaze system was entirely hands free.

Based on feedback from the study the system has undergone multiple reiterations to produce the updated system: iGAZE2 presented in this chapter. In this chapter the evolution of the eye gaze system from its initial benchtop platform to its current iteration is presented.

A benchtop study to assess the feasibility, intuitiveness, and workload of this system versus a conventional endoscope of iGAZE2 is then presented.

Aims of this Chapter:

1. Present the iterative process in the development of iGAZE2
2. Assess the intuitiveness and workload of the new system in novice users

8.2 Methodology

8.2.1 System Setup

8.2.1.1 Robotic Control System Evolution

The initial motorised system consisted of a large plastic panel with motors housed across its width with plastic inlays shaped to lie across the shaft of the endoscope. This was attached to the fixed robotic platform fastened to a mount which was not designed to be moved or held. The motor unit and endoscope were then attached to a fully robotised arm to insert and withdraw the endoscope (Figure 8.1).

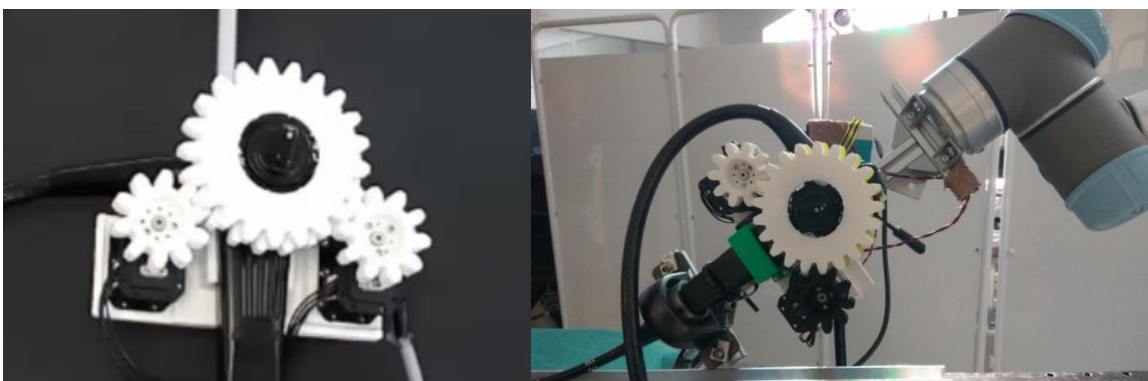


Figure 8.1 Original Eye Gaze steering wheel mount (left) and robotised arm (right).

This system took up a significantly large footprint. To allow practical use in a real world setting, the system was redesigned to allow it to be held by the operator, and take up a smaller footprint. To allow this, the simple cog wheel setup used in the original setup was revised with a more robust, and smaller setup designed. The first iteration included a thinner steering wheel mount which during trials was prone to slippage of the motor belt and detachment of the steering wheel from the motor system (Figure 8.2).

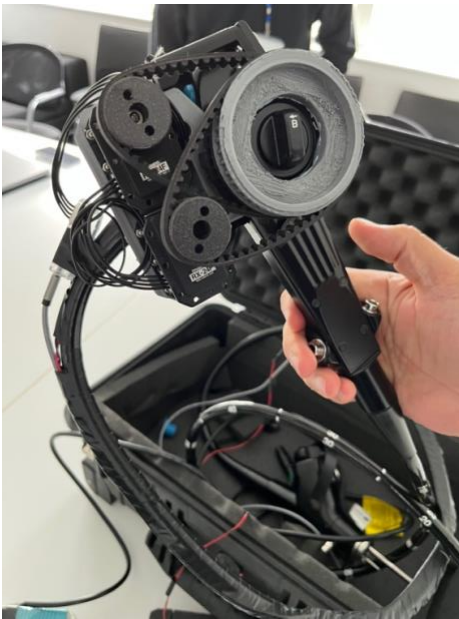


Figure 8.2 Eye Gaze steering wheel mount with thinner steering wheel.

A thicker steering wheel mount with raised edges was subsequently used with a side-to-side configuration. This setup was robust during trials with no slippage of the steering belt but did not allow access to the endoscope button and valves (Figure 8.3).



Figure 8.3 Eye Gaze steering wheel mount with thicker steering wheel and side to side mount (left) and in use (right).

Therefore, the system was reconfigured to be rear-mounted with the motorised complex attached to the rear of the endoscope, with full access to the endoscope button and valves. This allowed air insufflation, suction and photo capture to be operated by the endoscopist with the system in place (Figure 8.4).

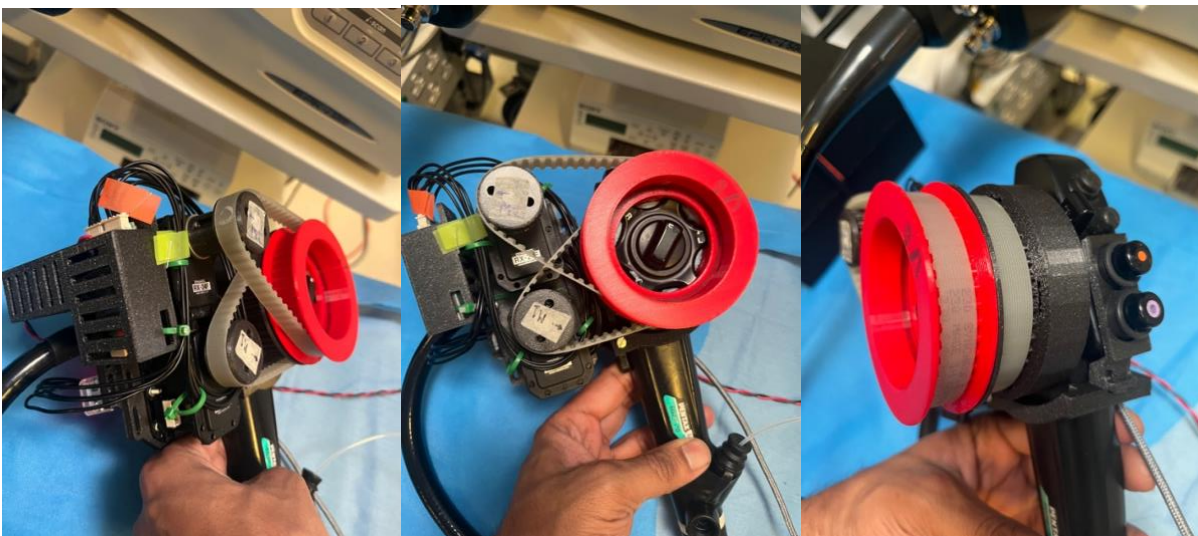


Figure 8.4 Eye Gaze steering wheel mount with rear attachment from three angles.

As prior, the 3D printed gears were placed over the endoscope steering wheels and actuated by small Dynamixel motors (Dynamixel RX-24F, Robotis, Korea). The system is designed so that the wheel and belt are easily to both remove and attach. This allows the endoscope to be controlled conventionally with the motors mounted. The belt and wheel can then be attached when the system is to be used. This was designed to allow conventional endoscope intubation and rapid conversion to the iGAZE2 system through simply mounting the wheel and 2 belts (Figure 8.5). For this trial the unit was attached to the shaft of a Pentax EG29-i10 Video Gastroscope.



Figure 8.5 Endoscope with iGAZE2 system partially mounted for intubation (left) and with wheel and belts attached (right).

8.2.1.2 Gaze Control evolution

The initial eye tracking system used a custom gaze-contingent framework developed by Kogkas et al. (292) (293). The initial eye tracking glasses had spherical markers attached with one RGB-D camera and four ceiling mounted Optitrak cameras (Optitrak, Corvallis, Oregon, USA) to allow

the entire user body position to be recognised as an input for the insertion and withdrawal function, controlled by the robotic arm. Simplification of the system allowed this to be reduced to the modern lightweight eye-tracking glasses (Pupil Core, Pupil Labs, Berlin, Germany), weighing just 22.75g with no external cameras. These glasses feature two inward-facing cameras that track pupil movement and one outward-facing camera capturing the user's field of view.

8.2.3 User Interface

The operator sat or stood 2 metres away from the monitor with the monitor placed slightly below the endoscopists eye line as reported to be the most ergonomically favourable position. A calibration was performed requiring the user to trace 9 targets around the outside perimeter and centre of the monitor. The user was able to insert and withdraw the scope manually with one hand. Steering was controlled by the direction of gaze. For example, if the user looked to the top right of the monitor the endoscope tip would move so the point of focus was now central on the monitor screen. A foot pedal was added to allow automatic retroflexion following deployment of the pedal for 2 seconds (Figure 8.6).



Figure 8.6 Foot pedal used to control retroflexion with two additional unmapped pedals.

Calibration

Calibration was performed requiring the user to trace targets around the outside perimeter and centre of the monitor. Calibration accuracy was trialled at different durations with an optimal calibration found to be 60 seconds as opposed to the 20 seconds used in benchtop trials. (Figure 8.7).

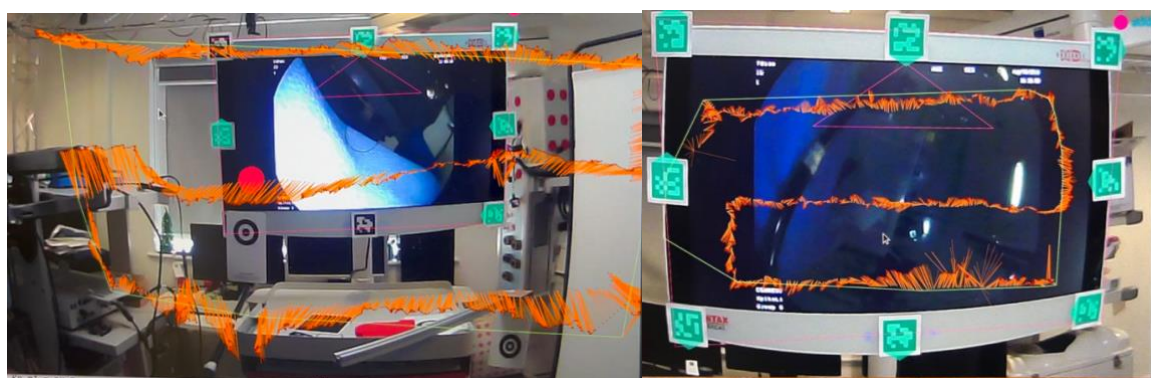


Figure 8.7 Calibration over 20 seconds (left) and 60 seconds (right).

The user inserts and withdraw the endoscope with the right hand and steers the endoscope tip using the direction of gaze. For example, looking to the left of the screen would steer the endoscope tip until the point of the focus was the centre of the monitor. Previously a joypad had been used to control retroflexion, but this was converted to a foot pedal as this fit into the conventional endoscopy workflow where foot pedals are used to control water irrigation and diathermy during therapeutic endoscopy. The foot pedal could be pressed to allow automatic retroflexion and then again to allow deflexion of the scope. Two additional pedals were available on the unit which theoretically could be mapped to other use functions (Figure 8.6).

8.2.4 Study Design

This study was a controlled trial to compare iGAZE2 to a conventional endoscope in novices, in terms of performance and user workload.

Twelve participants with no previous endoscopy, or gaze control experience were recruited. The age range of the group was 24 – 38years. The mixed group consisted of doctors (foundation trainees, an internal medical trainee and a microbiologist), engineers, non-clinical scientists and an advertising executive.

Participants were randomised to begin on either the gaze control system or the conventional endoscope. Each participant was given a standardised 2-minute instruction by the author (AS) on the system they were first using and a standardised explanation of the benchtop task.

The benchtop task consisted of an anatomically accurate model of the stomach in a closed black box (Figure 8.8). Within the stomach 9 numbered targets were placed at various points including fundus, body and pylorus. The participant was then required to complete retroflexion to visualise the gastric cardia.

Each task began with the endoscope tip placed at the ‘gastro-oesophageal junction’. The endoscopist was then required to locate the numbered targets from 1-9 in sequential order by placing the target in the central view. The central view was delineated with a 4cm diameter circle placed in the centre of the monitor. Participants were required to place the targets in the central view and ‘en face’.

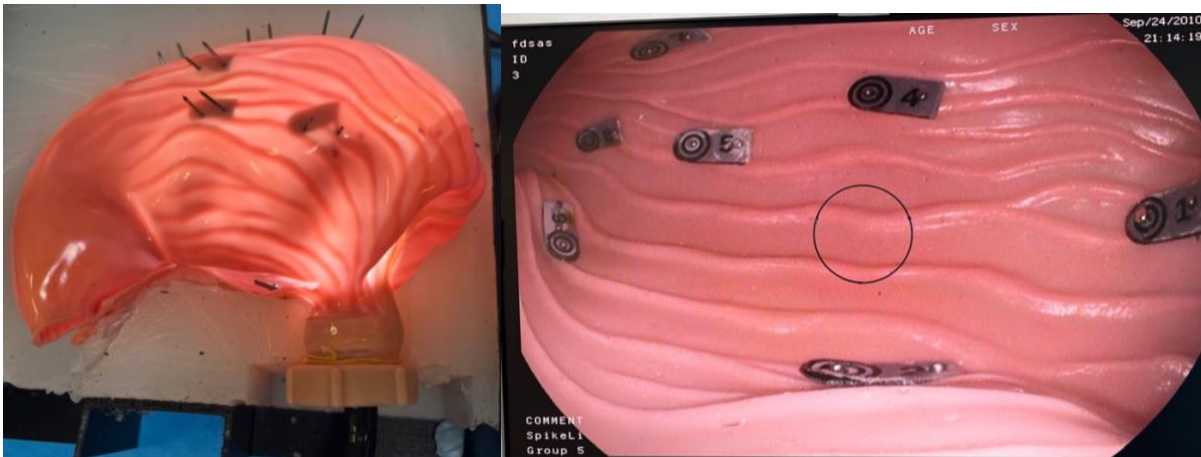


Figure 8.8 Anatomical stomach with box removed (left), monitor view of stomach model with targets with central target which number must be placed in(right)

Each participant completed the task five times and then transferred to the alternate system with a standardised instruction on the second system prior to completing the task five times again. Times were recorded and subjective feedback for each system was acquired directly after completing the task with each system to avoid recall bias.

Outcomes

8.2.5 Objective outcomes

The total time to find all targets, the time to complete retroflexion and the total time of each task was recorded.

8.2.6 Subjective feedback

Subjective feedback on the workload of each system was collected using the raw NASA-TLX score (296). The NASA-TLX score has been validated in assessing workload in both diagnostic

and therapeutic endoscopy (296,299). This is a ten-point analogue scale validated in both diagnostic and therapeutic endoscopy. The NASA TLX score domains included mental demand, physical demand, temporal demand, effort and frustration. The domain 'performance' was removed as this was measured objectively. The data was collected with the official NASA-TLX ios (iphone operating system) application.

8.2.7 Data analysis

All times were recorded as mean +/- standard deviation to 2 decimal places. Total task times were taken as an average of the 5 times recorded per system. NASA TLX scores were reported to 1 decimal place.

All comparisons were conducted using within subject analysis. The following comparisons were undertaken:

- Task completion time of iGAZE2 versus conventional control.
- Retroflexion time of iGAZE2 versus conventional control.
- Total NASA-TLX scores of iGAZE2 versus conventional control.
- NASA-TLX subdomain scores (mental demand, physical demand, temporal demand, effort and frustration) of iGAZE2 versus conventional control.

The paired t test with two tails was used to compare the normally distributed groups. A p value below 0.05 was used to denote significance.

8.3 Results

8.3.1 Completion Times

Participants were significantly quicker completing the task using iGAZE2 versus a conventional endoscope (65.02 +/- 16.34s vs 104.21 +/- 51.31s, $p=0.013$) (Figure 8.9).

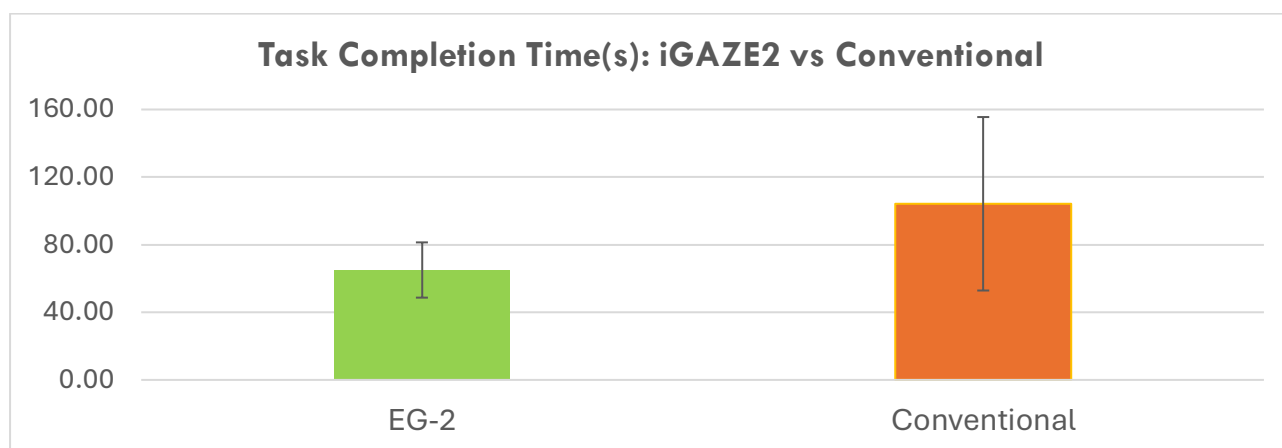


Figure 8.9 Task completion time in seconds of iGAZE2 versus Conventional (with standard deviations).

Participants were also significantly quicker completing retroflexion using iGAZE2 versus a conventional endoscope (8.48 +/- 3.08 vs 11.38 +/- 5.36s, $p=0.036$) (Figure 8.10).

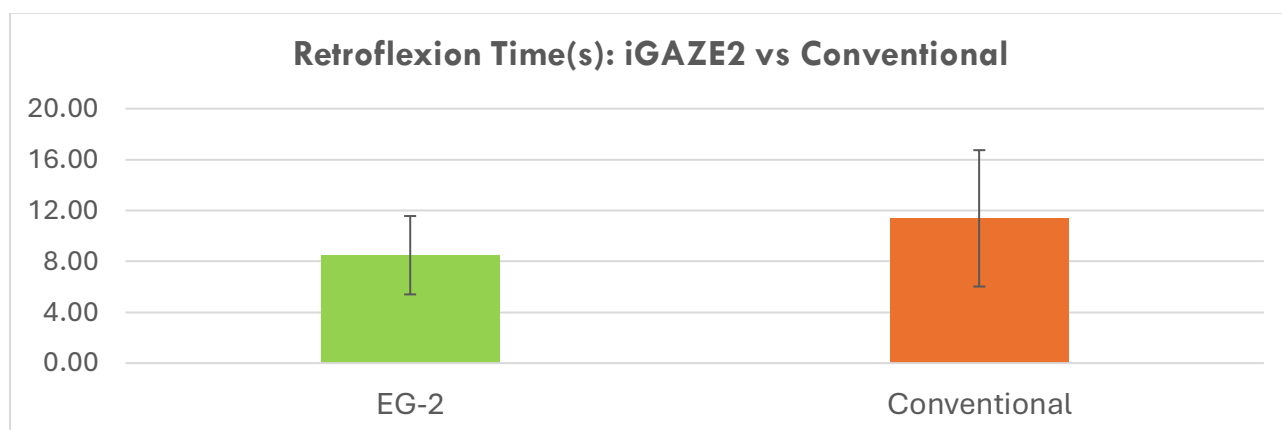


Figure 8.10 Retroflexion time in seconds of iGAZE2 versus Conventional (with standard deviations).

8.3.2 Workload Scores

Participants reported a significantly lower workload (raw NASA-TLX score) when using iGAZE2 versus the conventional endoscope (152.1 +/- 63.4 vs 319.6 +/- 81.6, $p=0.0001$) (Figure 8.11).

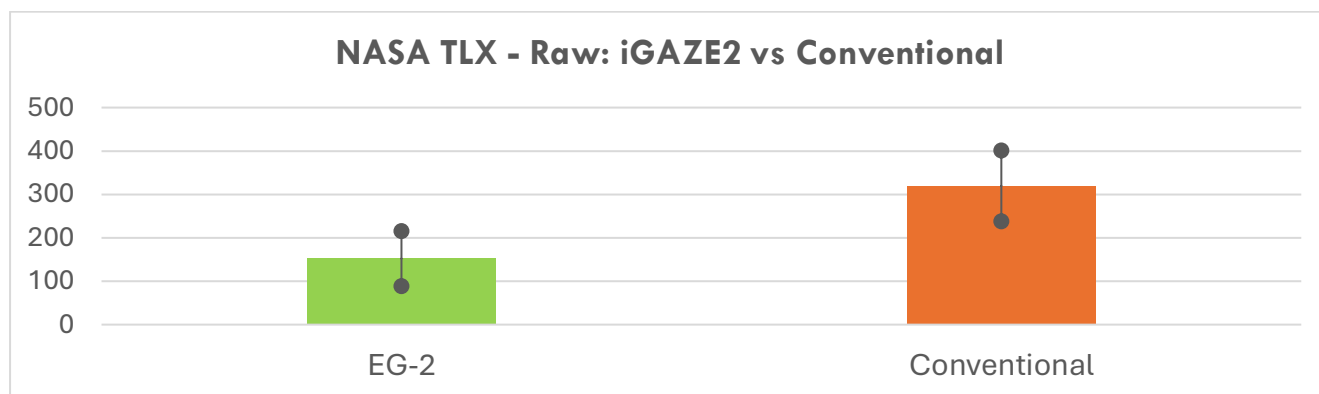


Figure 8.11 NASA TLX score of iGAZE2 versus Conventional (with standard deviations).

For all subdomains users found iGAZE2 to have a lower temporal demand: (30.0 +/- 14.0 vs 67.1 +/- 15.9, $p=0.0001$), mental demand (34.2 +/- 16.6 vs 60.0 +/- 26.1, $p=0.0165$), effort (40.0 +/- 19.8 vs 71.7 +/- 16.3, $p=0.0006$), mental demand (34.2 +/- 16.6 vs 60.0 +/- 26.1, $p=0.0165$), physical demand (24.6 +/- 20.9 vs 63.3 +/- 26.0, $p=0.0001$) and frustration (27.9 +/- 20.3 vs 57.5 +/- 21.1, $p=0.0079$) (Figure 8.12).

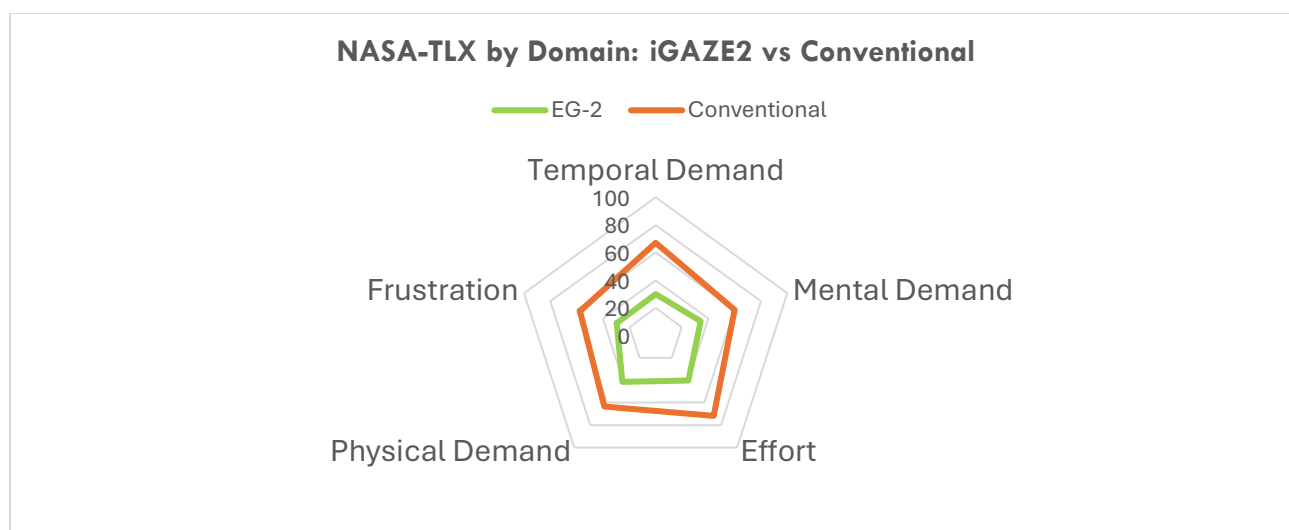


Figure 8.12 Radar Plot of NASA TLX subdomains of iGAZE2 versus Conventional (with standard deviations).

8.4 Discussion

We present the trial data of iGAZE2, an updated eye controlled robotised endoscope control system. The previous trial using the original system proved the feasibility of an eye controlled robotised endoscope control system. The trial also suggested the system may be more intuitive but was not designed to answer this question. The trial design of this new study used only novices and allowing us to ascertain the comparative intuitiveness of iGAZE2 versus conventional endoscopy through both objective and subjective measures.

All users were significantly quicker using iGAZE2 suggesting that iGAZE2, a gaze-controlled system was more intuitive denoted by the improved performance. The addition of a foot pedal also proved to be a more intuitive method to control retroflexion with significantly quicker completion of retroflexion with iGAZE2.

All users reported a significantly lower workload across all domains suggesting further the intuitiveness of iGAZE2 versus conventional endoscopy. In the previous trial this has been true other than for physical demand. The previous system used head tilting and body movement to control rotation and insertion of the endoscope. This was removed in iGAZE2 with insertion and withdrawal controlled by the right hand. This update seemed to improve the workload further with a significant lower physical demand in iGAZE2 versus conventional endoscopy.

The new platform involves a combination of gaze and manual control. Only one hand is needed to insert and withdraw the endoscope leaving the other hand free. The other hand could be used to control instruments which currently is performed by a second person requiring the endoscopist to communicate and be reliant on assistant to perform critical tasks such as knife

deployments, snare closure and coagulation grasping. When the endoscopist has the area of interest in the field of view all tip control could be done hands free with only intermittent use of the right hand to withdraw or insert the endoscope if needed during the intervention. The previous iteration was entirely hands free but introduction of the combined controlled system is demonstrated to still have a significantly improved performance and workload versus the conventional endoscope control system.

Limitations of this study include the simulated environment which does not truly represent the deformability and peristalsis seen in real endoscopy. Lower gastrointestinal endoscopy has different requirements including torque steering and therefore the outcomes cannot be applied to lower endoscopy.

8.5 Conclusion

The remit of endoscopy continues to grow requiring precision control via the conventional despite its well documented non intuitive and poor ergonomic control system. There has been much work on modernising the control system through use of robotics. The new iteration of our gaze control system has proved to be a more intuitive control system than conventional endoscopy and is the only system we are aware of using gaze as a control input. The tip control remains hands free but insertion is now manual. This study has shown it remains favourable as a control system to a conventional endoscope. The updated system has a significantly smaller footprint and due to its setup can be fitted to any conventional endoscope through printing different 3D gears at a low cost. This system represents a further exciting step in this novel endoscope control system.

9. iGAZE2 – Human Trial

Content from this chapter is under review for publication.

9.1 Background

In the previous chapters a novel gaze controlled endoscope robotic system that can be retrofitted to any endoscope to allow gaze controlled endoscope tip steering has been presented. Initial benchtop trials demonstrated the technologies feasibility(286). Subsequent refinement was undertaken and the iGAZE 2 system was trialled in a benchtop environment demonstrating that the system was more intuitive to use than a conventional endoscope(305). In this chapter the evolution of the eye gaze system from its initial benchtop platform to its current human use iterated system is presented.

Aims of this Chapter:

1. Assess the feasibility of the iGAZE2 system in human use
2. Assess the safety of the iGAZE2 platform

9.2 Methodology

9.2.1 System Setup

The iGAZE 2 system was setup as described in Chapter 8.

9.2.1.4 Room Setup

The endoscopist sat next to the head of the patient facing the monitor (Figure 9.1). Although the seated position is less used in the Western world it is a commonly used setup in the East to provide better ergonomics for the therapeutic endoscopist.



Figure 9.1 Left – Room Setup without patient or endoscopist, Right – setup with endoscopist and patient (not shown)

The bed was placed at the left of the endoscopist similar to normal endoscopic room setup allowing ease of access for the nurses (Figure 9.2).



Figure 9.2 Room Setup showing bed position relative to endoscopist's seat.

9.2.2 Study Design

This was a prospective clinical trial to assess the feasibility of the iGAZE2 system as an endoscope control system during an UGI endoscopy. The study was sponsored by Imperial College London and approved by the Health Research Authority North West – Greater Manchester South Research Ethics Committee on the 4th March 2022 (IRAS 288108) (Appendix 4).

Three patients requiring a diagnostic endoscopy were recruited in outpatients and their suitability was assessed by the study leads. A patient information sheet, approved by the ethics committee, was provided.

On the day of the procedure participants were consented conventionally for an endoscopy and for the trial including the sharing of data and images. A formal briefing took place involving the endoscopist, engineering staff and endoscopy nursing team.

After calibration of the system the patient was brought into the room and the standard safety checks were undertaken including confirming the patient identity, consent and procedure. Participants were given sedation as per the British Society of Gastroenterology guidance (306).

The initial intubation of the endoscope to the oesophagus was completed manually with the iGAZE2 system partially applied. Once in the oesophagus the system was then attached by the engineering team. The gaze control system was then used to attempt to progress into the stomach and the duodenal bulb and to complete retroflexion within the stomach to visualise the gastro-oesophageal junction. The system was then removed to allow extubation of the endoscope or completion of any parts of the endoscopy not done with the robotic system.

9.2.3 Outcomes

Objective outcomes

The success of the iGAZE2 system to access the stomach, duodenal bulb and complete retroflexion was assessed. The total time for the procedure and was measured. The time to attach the iGAZE2 system was recorded. Doses of medication given were documented. Adverse events or complications were noted.

Subjective feedback

The patient discomfort score was agreed by the endoscopy nurses and endoscopists and recorded (as per standard endoscopic practice).

Data analysis

All times were recorded as mean +/- standard deviation to the nearest second.

9.3 Results

9.3.1 Participants

Participants ranged between 26 and 61 years of age. Participant one was a male referred with symptoms of oesophageal reflux, participant two was a female referred with resistant helicobacter pylori infection requiring cultures and participant three was a female referred with dyspepsia.

9.3.2 Objective Outcomes

Progression into the stomach and retroflexion was successful in all three patients. Intubation of the duodenal bulb was successful in two out of the three patients. One patient required biopsies which was done whilst using the iGAZE2 system and the operator successfully operating the instrument (Figure 9.3 and Table 9.1).

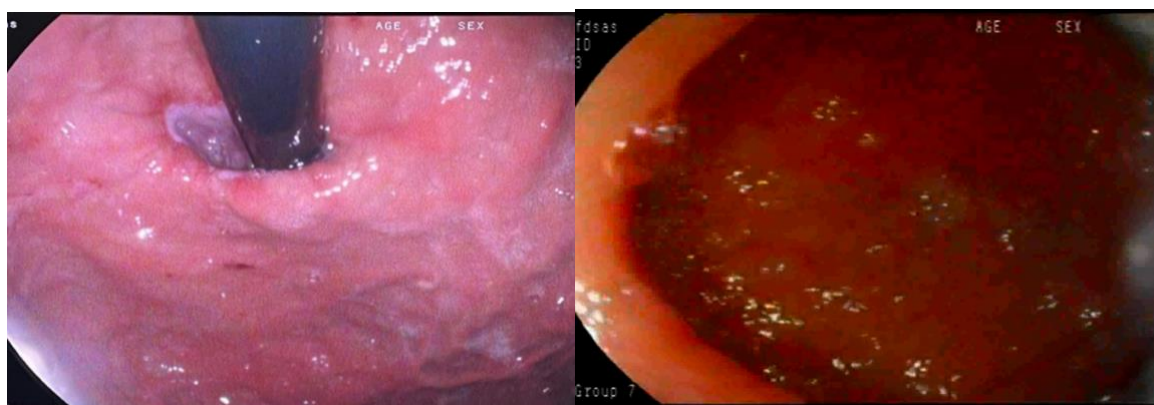


Figure 9.3 Left – retroflexion using the iGAZE2 system (patient 2), Right – D1 intubation using the iGAZE2 system (patient 3).

Patient 1	Patient 2	Patient 3
-----------	-----------	-----------

D1 intubation	N	Y	Y
Retroflexion	Y	Y	Y
Intervention	NA	Biopsies	NA

Table 9.1 Table showing success of intubation, retroflexion and intervention (where applicable).

Attachment of the system took between 49 to 72 seconds (59.7s +/- 11.6). The total time of endoscopy was between 12 minutes and 22 seconds and 14 minutes and 10 seconds (13:07 +/- 56.0s) (Table 9.2).

	Patient 1	Patient 2	Patient 3
Total seconds	850	770	742
System attachment (sec)	72	58	49

Table 9.2 Table showing total time and time of system attachment in each patient.

Pain scores ranged between 1 (comfortable throughout) and 2 (mild discomfort, well tolerated). The median doses of midazolam, fentanyl and xylocaine were 3mg, 75mcg and 100mg respectively meeting national sedation standards (being <5mg midazolam and <100mcg fentanyl) (Table 9.3).

	Patient 1	Patient 2	Patient 3
Age	61	26	54
Fentanyl (mcg)	75	100	75
Midazolam (mg)	3	4	3
Xylocaine (mg)	100	100	100
Pain score	Well tolerated	Mild discomfort	Well tolerated

Table 9.3 Table showing pain score and medication dosing with ages of patients..

There were no adverse events or complications.

9.4 Discussion

This trial represents the first human trial of a gaze-controlled endoscope which demonstrates the system's feasibility. Previous trials of this system have demonstrated the system was more intuitive to novice users compared to a traditionally controlled endoscope but were conducted in a benchtop environment.

This trial has demonstrated iGAZE2 is a feasible control system in human endoscopy with retroflexion being successful in all patients and duodenal intubation in the majority. As this was the first ever human trial the ethics understandably limited the scope of the gaze control. There was therefore no experience of intubating the oesophagus with the control system or navigating to the second part of the duodenum. However, the ability to successfully navigate from oesophagus to duodenum and complete retroflexion using the system is promising.

Comparative data was lacking due to the small numbers and single operator. It was felt appropriate however, given the first ever human use of the system, that a small number of participants were recruited and a single operator most familiar with both iGAZE2 and the conventional endoscope was used for this feasibility trial.

This platform utilised gaze control for tip steering and one hand to insert and withdraw the endoscopy leaving one hand free. When using instruments, traditionally the operator must instruct the assistant to use the tools, adding an extra step with potential errors. iGAZE2 allows the operator to use endoscope instruments themselves taking a potential chain of error out of

interventional procedures. In one case the operator was able to use the instrument themselves to take biopsies successfully demonstrating this system advantage.

Previous benchtop trials have shown that iGAZE2 is a more intuitive system and presumably therefore has a lower workload. The availability of the second hand and lack of needing to communicate and rely on an assistant may further reduce the workload of complex therapeutic interventions.

9.5 Conclusion

The iGAZE2 system heralds a potentially exciting simple, small and retrofittable system that can reduce cognitive workload through an intuitive steering system and the liberation of one hand. This first human trial is an exciting beginning demonstrating the feasibility of the system in human use. Further work can now be progressed following this safe demonstration.

10. Main thesis outcomes and future directions

10.1 Main outcome of this thesis

Gastrointestinal endoscopy is in one of its most exciting phases, with rapid technological advancement being translated into high quality patient care. There is no area of endoscopy that isn't undergoing innovation, whether it be technological advancement of the equipment or using current endoscopy equipment to deliver more novel and innovative interventions.

We have always been looking at the same mucosa with an endoscope, but through innovation of imaging technology we are seeing more there than we ever have. Early detection of precancerous lesions has been met by the advancement of therapeutic endoscopy allowing curative resections through minimally invasive techniques that would have required complex surgery and gruelling medical therapies.

Innovators will continue to push this advancement, and practitioners will translate this into exponentially improving patient care. Tragic stories of missed cancer or complicated surgery are being translated into simple and standard day case procedures. It is no exaggeration to say endoscopy research and the resultant improvement of both diagnostic and therapeutic endoscopy is lifesaving

As a clinician providing and training in therapeutic endoscopy, I have relished the opportunity to research such a fundamental area of my clinical practice. To find an area of novel interest in such a rapidly developing and researched field has been stimulating. Little focus has been placed on the role of vision and gaze in endoscopy, a key but neglected node in the workstream of the endoscopy procedure.

In chapter 2 a review of the young but evolving area of gaze tracking in endoscopy was presented. This chapter allowed me to develop an understanding of eye tracking and recognise it as fertile ground for endoscopic innovation. Its use to track eye patterns as an investigative tool became

apparent but this search for use-cases instilled the first thoughts of the application of gaze for something other than eye tracking analysis alone.

Artificial intelligence and its real-world applications have been one of, if not the most rapid technological innovations across all discipline and fields. It is hard to think of an area that the broad extent of its reach has not touched in our lives. Vision plays a vital role in the diagnostic capability of the endoscopist with early detection translating to early treatment and appropriate surveillance of GI pathology. The potential role of CADe emerged during my research period and there were countless data in benchtop or simulated environments. I was proud to deliver one of the first international meta-analyses of its real-world outcomes to demonstrate its real-world benefit.

Orientation in endoscopy is reliant on processing of images through vision and cognitive translation. The flexibility of the endoscope and mental workload of the procedure challenge successful orientation yet this is an understudied area of endoscopy. Chapter 4 allowed me to evaluate practising endoscopists and demonstrated the disorientation experienced by a large percentage of endoscopists.

This base work in chapters 2-4 showed me the importance of gaze and orientation in endoscopy but also the potential role of AI. It also provided me a base to consider in chapters 5-6 the potential of gaze as a control system which prompted an exploration of the endoscope control system, its role in therapeutic endoscopy, available adjuncts and the exciting robotic endoscope platforms under development.

This extensive review of these novel areas allowed me to bring this learning together to innovate and use gaze tracking as a control system to develop a potentially intuitive control system for the challenging and dated conventional endoscope. Available robotic platforms are exciting, but due to footprint and cost, are not realistic systems for real-world use. Developing a system that was retrofittable to endoscopes in a cheap and simple way was a key target of this project. Initial feasibility of this novel system was demonstrated in chapter 7. Pragmatism and refinement however allowed us to iterate the system resulting in iGAZE2 which during its more extensive

benchtop trial confirmed categorically its more intuitive control system versus a conventional endoscope.

I am thankful to the Health Research Association and Research Ethics committee for approving our application for the first in vivo trial of a gaze-controlled endoscope system. Taking a benchtop system to its first human trial and demonstration of its feasibility in humans was a privilege and a validation of the base work taking us to this moment.

This thesis has allowed me to develop my skills in reviewing, analysing and critically appraising available data, conduct my own trials, gain ethical approval and deliver a human trial. This process has allowed me to collaborate with highly skilled and capable colleagues across disciplines. Most importantly this project has allowed me to collaborate with technologically astute and intelligent engineers and collaboratively translate innovative benchtop technologies into real human applications.

The NHS may have its critics but there are no other environments that would have provided a clinician with the support to deliver such a collaborative project culminating in a human trial of a novel endoscopic robotic platform.

10.2 Future perspectives

The value of endoscopy in patient care cannot be understated and its quality, role and remit continue to evolve rapidly. An aging and growing population rightly demand higher quality care. The success of endoscopy is multifaceted, but technology plays a key role. The endoscopists themselves are critical and their high-quality training vital. But technology can help through reducing the cognitive demands on endoscopists. Techniques such as ESD have a demonstrably positive effect on patient outcomes but require significant training and high cognitive workload.

The iGAZE2 system is a more intuitive control system than a conventional endoscope that may reduce some of the cognitive demands on an endoscopist. As with any new technology this system is a proof of concept that will need refinement and further iteration before it is a

deliverable real-world control system, but all advancements must start somewhere. Its potential applications are myriad. In gaze controlled diagnostic endoscopy an endoscopist can pay more attention to the examination itself reducing the chances of missed lesions and increasing the chances of early diagnoses. During therapeutic endoscopy gaze control will allow intuitive repositioning of the endoscope to facilitate interventions whilst freeing the steering hand to control endoscope instruments themselves, rather than relying on a second person, removing a step with potential for errors.

The addition of CADe to a gaze-controlled system would improve lesion detection and could further reduce cognitive demand on endoscopists. The incorporation of AI to refine the control system and both use the input of gaze, analysis of the endoscope position and the visible mucosa on screen against a learned database of endoscopy videos may improve the systems navigation and steering.

Ultimately the successful integration of various technologies including gaze control, soft robotics and AI may successfully produce an endoscope control system with a reduced cognitive workload through more intuitive steering and allowing focus to be directed to diagnosis and therapeutics. Such a system would also allow complex yet beneficial techniques confined to a small number of highly skilled and trained endoscopists to be accessible to more endoscopists.

10.3 Conclusion

The role of endoscopy continues to widen despite the same basic control system since its inception half a century ago. Gaze technology is a novel and exciting area for endoscopy. This thesis has shown the potential of a retrofittable gaze control system, its increased intuitiveness from a benchtop theoretical system to successful use in a human trial.

It is hard to predict the exact future of the endoscope control system but it easy to predict that with the rapid evolution of endoscopy technology; it will not be the decades old control system used by the majority of endoscopist today. The future of endoscopy and the potential improvements for patient care globally is exciting.

11. References

1. Sivananthan A, Ahmed J, Kogkas A, Mylonas G, Darzi A, Patel N. Eye tracking technology in endoscopy: Looking to the future. *Digestive Endoscopy*. 2023;35(3): 314–322. <https://doi.org/10.1111/den.14461>.
2. Meeks RK, Anderson J, Bell PM. Physiology Of Spatial Orientation. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2025. <http://www.ncbi.nlm.nih.gov/books/NBK518976/> [Accessed 29th March 2025].
3. Kamran U, King D, Abbasi A, Coupland B, Umar N, Chapman WC, et al. A root cause analysis system to establish the most plausible explanation for post-endoscopy upper gastrointestinal cancer. *Endoscopy*. 2023;55(02): 109–118. <https://doi.org/10.1055/a-1917-0192>.
4. Huang J, Koulaouzidis A, Marlicz W, Lok V, Chu C, Ngai CH, et al. Global Burden, Risk Factors, and Trends of Esophageal Cancer: An Analysis of Cancer Registries from 48 Countries. *Cancers*. 2021;13(1): 141. <https://doi.org/10.3390/cancers13010141>.
5. *Survival Rates for Esophageal Cancer | Esophageal Cancer Outlook*. <https://www.cancer.org/cancer/types/esophagus-cancer/detection-diagnosis-staging/survival-rates.html> [Accessed 5th January 2024].
6. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. *The Lancet*. 2013;381(9864): 400–412. [https://doi.org/10.1016/S0140-6736\(12\)60643-6](https://doi.org/10.1016/S0140-6736(12)60643-6).
7. Eslick GD. Epidemiology of Esophageal Cancer. *Esophageal Cancer*. 2009;38(1): 17–25. <https://doi.org/10.1016/j.gtc.2009.01.008>.
8. Coleman HG, Xie SH, Lagergren J. The Epidemiology of Esophageal Adenocarcinoma. *Gastroenterology*. 2018;154(2): 390–405. <https://doi.org/10.1053/j.gastro.2017.07.046>.
9. Xie SH, Lagergren J. Risk factors for oesophageal cancer. *Oesophageal cancer*. 2018;36–37: 3–8. <https://doi.org/10.1016/j.bpg.2018.11.008>.
10. Fitzgerald RC, Di Pietro M, Ragunath K, Ang Y, Kang JY, Watson P, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett’s oesophagus. *Gut*. 2014;63(1): 7–42. <https://doi.org/10.1136/gutjnl-2013-305372>.
11. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*. 2021;71(3): 209–249. <https://doi.org/10.3322/caac.21660>.
12. Morgan E, Arnold M, Camargo MC, Gini A, Kunzmann AT, Matsuda T, et al. The current and future incidence and mortality of gastric cancer in 185 countries, 2020–40: A population-based modelling study. *eClinicalMedicine*. 2022;47. <https://doi.org/10.1016/j.eclinm.2022.101404>.

13. *Stomach cancer statistics*. Cancer Research UK.
<https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer> [Accessed 5th January 2024].
14. Banks M, Graham D, Jansen M, Gotoda T, Coda S, Pietro M di, et al. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. *Gut*. 2019;68(9): 1545–1575. <https://doi.org/10.1136/gutjnl-2018-318126>.
15. Zullo A, Hassan C, Romiti A, Giusto M, Guerriero C, Lorenzetti R, et al. Follow-up of intestinal metaplasia in the stomach: When, how and why. *World Journal of Gastrointestinal Oncology*. 2012;4(3): 30–36. <https://doi.org/10.4251/wjgo.v4.i3.30>.
16. LAHNER E, BORDI C, CATTARUZZA MS, IANNONI C, MILIONE M, DELLE FAVE G, et al. Long-term follow-up in atrophic body gastritis patients: atrophy and intestinal metaplasia are persistent lesions irrespective of *Helicobacter pylori* infection. *Alimentary Pharmacology & Therapeutics*. 2005;22(5): 471–481. <https://doi.org/10.1111/j.1365-2036.2005.02582.x>.
17. World Health Organisation. *International Agency for Research on Cancer. Cancer Today Globocan 2018*. <http://gco.iarc.fr/today/fact-sheets-cancers>. [Accessed 20th October 2019].
18. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66(4): 683–691. <https://doi.org/10.1136/gutjnl-2015-310912>.
19. Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, Ballegooijen M van, Hankey BF, et al. Colonoscopic Polypectomy and Long-Term Prevention of Colorectal-Cancer Deaths Ann. *The New England Journal of Medicine*. 2012;366(8): 687–696.
20. Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, et al. Adenoma detection rate and risk of colorectal cancer. *The New England Journal of Medicine*. 2014;370: 1298–1306. <https://doi.org/10.1016/j.bpg.2017.07.002>.
21. 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. <https://doi.org/10.1053/j.gastro.2013.09.001>.
22. Kahi CJ, Myers LJ, Slaven JE, Haggstrom D, Pohl H, Robertson DJ, et al. Lower endoscopy reduces colorectal cancer incidence in older individuals. *Gastroenterology*. 2014;146(3): 718-725.e3. <https://doi.org/10.1053/j.gastro.2013.11.050>.
23. Anderson R, Burr NE, Valori R. Causes of Post-Colonoscopy Colorectal Cancers Based on World Endoscopy Organization System of Analysis. *Gastroenterology*. 2020;158(5): 1287-1299.e2. <https://doi.org/10.1053/j.gastro.2019.12.031>.
24. Bozzini P. Lichtleiter, eine Erfindung zur Anschauung innerer Teile und Krankheiten, nebst der Abbildung" [Light conductor, an invention for examining internal parts and diseases,

together with illustrations]. *Journal der Practischen Arzneykunde und Wundarzneykunst*. 1806;24: 107–124.

25. Newell OK. The Endoscopic Instruments of Joseph Leiter of Vienna and the Present Development of Endoscopy. *The Boston Medical and Surgical Journal*. 1887;117: 528–530.
26. Hirschowitz BI. Development and Application of Endoscopy. *Gastroenterology*. 1993;104(2): 337–342.
27. Spurr Jr. C. History of the Instruments and Techniques of Gastrointestinal Endoscopy. In: Sridhar S, Wu G (eds.) *Diagnostic and Therapeutic Procedures in Gastroenterology: An Illustrated Guide*. Springer International Publishing; 2018. p. 3–13.
28. 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. *Therapeutic Advances in Gastroenterology*. 2018;11: 1–12. <https://doi.org/10.1177/1756284818814948>.
29. Hassan C, Pickhardt PJ, Rex DK. A resect and discard strategy would improve cost-effectiveness of colorectal cancer screening. *Clinical Gastroenterology and Hepatology*. 2010;8(10): 865-869.e3. <https://doi.org/10.1016/j.cgh.2010.05.018>.
30. Williet N, Tournier Q, Vernet C, Dumas O, Rinaldi L, Roblin X, et al. Effect of Endocuff-assisted colonoscopy on adenoma detection rate: Meta-analysis of randomized controlled trials. *Endoscopy*. 2018;50(9): 846–860. <https://doi.org/10.1055/a-0577-3500>.
31. Triantafyllou K, Gkolfakis P, Tziatzios G, Papanikolaou IS, Fuccio L, Hassan C. Effect of Endocuff use on colonoscopy outcomes: A systematic review and meta-analysis. *World Journal of Gastroenterology*. 2019;25(9): 1158–1170. <https://doi.org/10.3748/wjg.v25.i9.1158>.
32. Jian HX, Feng BC, Zhang Y, Qu JY, Li YY, Zuo XL. Endocuff-assisted colonoscopy could improve adenoma detection rate: A meta-analysis of randomized controlled trials. *Journal of Digestive Diseases*. 2019;(August): 1–11. <https://doi.org/10.1111/1751-2980.12814>.
33. Ngu WS, Bevan R, Tsiamoulos ZP, Bassett P, Hoare Z, Rutter MD, et al. Improved adenoma detection with Endocuff Vision: The ADENOMA randomised controlled trial. *Gut*. 2019;68(2): 280–288. <https://doi.org/10.1136/gutjnl-2017-314889>.
34. Ngu WS, Walls M, Bhandari P, Stokes C, Totton N, Hoare Z, et al. The B-ADENOMA Study: Bowelscope - Accuracy of Detection using Endocuff Optimisation of Mucosal Abnormalities: Study Protocol for randomised controlled trial. *Endoscopy International Open*. 2018;6(7): E872–E877. <https://doi.org/10.1055/a-0591-9308>.
35. Walls M, Brand A, Ngu WS, Stokes C, Sharp L, Hoare Z. *Endoscopy Orals*. 2019;68(Suppl 2): 2019.

36. van Keulen KE, Soons E, Siersema PD. The Role of Behind Folds Visualizing Techniques and Technologies in Improving Adenoma Detection Rate. *Current Treatment Options in Gastroenterology*. 2019;17(3): 394–407. <https://doi.org/10.1007/s11938-019-00242-5>.
37. MacLeod C, Monaghan E, Banerjee A, Jenkinson P, Falconer R, Ramsay G, et al. Colon capsule endoscopy. *Surgeon*. 2020;18(4): 251–256. <https://doi.org/10.1016/j.surge.2020.01.008>.
38. Postgate AJ, Burling D, Gupta A, Fitzpatrick A, Fraser C. Safety, reliability and limitations of the given patency capsule in patients at risk of capsule retention: A 3-year technical review. *Digestive Diseases and Sciences*. 2008;53(10): 2732–2738. <https://doi.org/10.1007/s10620-008-0210-5>.
39. Hosoe N, Limpas Kamiya KJL, Hayashi Y, Sujino T, Ogata H, Kanai T. Current status of colon capsule endoscopy. *Digestive Endoscopy*. 2020; 1–9. <https://doi.org/10.1111/den.13769>.
40. Riggs LA, Niehl EW. Eye Movements Recorded During Convergence and Divergence. *J. Opt. Soc. Am.* 1960;50(9): 913–920. <https://doi.org/10.1364/JOSA.50.000913>.
41. Tobii. *Tobii Pro 3*. <https://www.tobiipro.com/product-listing/tobii-pro-glasses-3/> [Accessed 4th March 2022].
42. Levy DL, Sereno AB, Gooding DC, O'Driscoll GA. Eye Tracking Dysfunction in Schizophrenia: Characterization and Pathophysiology BT - Behavioral Neurobiology of Schizophrenia and Its Treatment. In: Swerdlow NR (ed.) Berlin, Heidelberg: Springer Berlin Heidelberg; 2010. p. 311–347. https://doi.org/10.1007/7854_2010_60.
43. Tseng PH, Cameron IGM, Pari G, Reynolds JN, Munoz DP, Itti L. High-throughput classification of clinical populations from natural viewing eye movements. *Journal of Neurology*. 2013;260(1): 275–284. <https://doi.org/10.1007/s00415-012-6631-2>.
44. Majaranta P, R  ih   KJ. Twenty Years of Eye Typing: Systems and Design Issues. In: *Proceedings of the 2002 Symposium on Eye Tracking Research & Applications*. New York, NY, USA: Association for Computing Machinery; 2002. p. 15–22. <https://doi.org/10.1145/507072.507076>.
45. Harezlak K, Kasprowski P. Application of eye tracking in medicine: A survey, research issues and challenges. *Computerized Medical Imaging and Graphics*. 2018;65: 176–190. <https://doi.org/10.1016/j.compmedimag.2017.04.006>.
46. Lami M, Singh H, Dilley JH, Ashraf H, Edmondson M, Orihuela-Espina F, et al. Gaze patterns hold key to unlocking successful search strategies and increasing polyp detection rate in colonoscopy. *Endoscopy*. 2018;50(7): 701–707. <https://doi.org/10.1055/s-0044-101026>.
47. Karamchandani U, Erridge S, Evans-Harvey K, Darzi A, Hoare J, Sodergren M. Eye-Tracking Technology Differentiates Visual Gaze Patterns Between Trainee Endoscopists According To a Validated Objective Skills Assessment Scale. *Gastrointestinal Endoscopy*. 2020;91(6): AB113–AB114. <https://doi.org/10.1016/j.gie.2020.03.905>.

48. Edmondson MJ, Pucher PH, Sriskandarajah K, Hoare J, Teare J, Yang GZ, et al. Looking towards objective quality evaluation in colonoscopy: Analysis of visual gaze patterns. *Journal of Gastroenterology and Hepatology (Australia)*. 2016;31(3): 604–609. <https://doi.org/10.1111/jgh.13184>.
49. Almansa C, Shahid MW, Heckman MG, Preissler S, Wallace MB. Association between visual gaze patterns and adenoma detection rate during colonoscopy: A preliminary investigation. *American Journal of Gastroenterology*. 2011;106(6): 1070–1074. <https://doi.org/10.1038/ajg.2011.26>.
50. Patel M, Williams S, Gulati S, Emmanuel A, Thrumurthy S, Haji A, et al. Gaze Tracking Analysis by Endoscopist Skillset Reveals a Mechanism for Improved Adenoma Detection Rate: Influence of Linked Colour Imaging. *Gastrointestinal Endoscopy*. 2022;95(6S): 254.
51. Wenzke K, Chisholm P, Chen D, Kwon R. Changes in Visual Gaze Patterns During Colonoscopy Withdrawal Over Course of Fellowship Training. *The American Journal of Gastroenterology*. 2020;115(Supplement): 282.
52. Vilarino F, Ameling S, Lacey G, Ghosh A, Patchett S, Mulcahy H. Eye Tracking Search Patterns in Expert and Trainee Colonoscopists: A Novel Method of Assessing Endoscopic Competency? *Gastrointestinal Endoscopy*. 2009;69(5): 370.
53. Lee A, Chung H, Cho Y, Kim JL, Choi J, Lee E, et al. Identification of gaze pattern and blind spots by upper gastrointestinal endoscopy using an eye-tracking technique. *Surgical Endoscopy*. 2022;36(4): 2574–2581. <https://doi.org/10.1007/s00464-021-08546-3>.
54. He W, Bryns S, Kroeker K, Basu A, Birch D, Zheng B. Eye gaze of endoscopists during simulated colonoscopy. *Journal of Robotic Surgery*. 2020;14(1): 137–143. <https://doi.org/10.1007/s11701-019-00950-1>.
55. Ho KMA, Banerjee A, Lawler M, Rutter MD, Lovat LB. Predicting endoscopic activity recovery in England after COVID-19: a national analysis. *The Lancet Gastroenterology & Hepatology*. 2021;6(5): 381–390. [https://doi.org/10.1016/S2468-1253\(21\)00058-3](https://doi.org/10.1016/S2468-1253(21)00058-3).
56. Liu X, Zheng B, Duan X, He W, Li Y, Zhao J, et al. Detecting Task Difficulty of Learners in Colonoscopy. *Journal of Eye Movement Research*. 2021;14(2): 1–13. <https://doi.org/10.16910/JEMR.14.2.5>.
57. Kumahara K, Ikematsu H, Shinmura K, Murano T, Inaba A, Okumura K, et al. Objective evaluation of the visibility of colorectal lesions using eye tracking. *Digestive Endoscopy*. 2019;31(5): 552–557. <https://doi.org/10.1111/den.13397>.
58. Maehata T, Fujimoto A, Uraoka T, Kato M, Horii J, Sasaki M, et al. Efficacy of a new image-enhancement technique for achieving hemostasis in endoscopic submucosal dissection. *Gastrointestinal Endoscopy*. 2020;92(3): 667–674. <https://doi.org/10.1016/j.gie.2020.05.033>.

59. Kamba S, Fukuda A, Sumiyama K. Eye Movements and Task Load of Endoscopists While Using Computer-Aided Detection System for Colonoscopy. *Gastrointestinal Endoscopy*. 2022;95(6): AB222. <https://doi.org/10.1016/j.gie.2022.04.571>.
60. Novo ME, Kim DM, Requa J, Rael E, Samarasena JB, Rombaoa C, et al. The Gaze Project: Why AI-Assisted Gastroenterologists Outperform Non-AI-Assisted Gastroenterologists for Colon Polyp Detection. *Gastroenterology*. 2021;160(6): S-380. [https://doi.org/10.1016/s0016-5085\(21\)01622-x](https://doi.org/10.1016/s0016-5085(21)01622-x).
61. Troya J, Fitting D, Brand M, Sudarevic B, Kather JN, Meining A, et al. The influence of computer-aided polyp detection systems on reaction time for polyp detection and eye gaze. *Endoscopy*. 2022; <https://doi.org/10.1055/a-1770-7353>.
62. Sivananthan A, Nazarian S, Ayaru L, Patel K, Ashrafian H, Darzi A, et al. ID: 3525827 PERFORMANCE OF COMPUTER AIDED DETECTION SYSTEMS IN FLAT, SESSILE AND DIMINUTIVE ADENOMAS: A META-ANALYSIS. *Gastrointestinal Endoscopy*. 2021;93(6): AB197. <https://doi.org/10.1016/j.gie.2021.03.442>.
63. Zhao S, Wang S, Pan P, Xia T, Chang X, Yang X, et al. Magnitude, Risk Factors, and Factors Associated With Adenoma Miss Rate of Tandem Colonoscopy: A Systematic Review and Meta-analysis. *Gastroenterology*. 2019;156(6): 1661-1674.e11. <https://doi.org/10.1053/j.gastro.2019.01.260>.
64. Rutter MD, Beintaris I, Valori R, Chiu HM, Corley DA, Cuatrecasas M, et al. World Endoscopy Organization Consensus Statements on Post-Colonoscopy and Post-Imaging Colorectal Cancer. *Gastroenterology*. 2018;155(3): 909-925.e3. <https://doi.org/10.1053/j.gastro.2018.05.038>.
65. Rees C, Dekker E. Postcolonoscopy colorectal cancer: how low can we go? *Frontline Gastroenterology*. 2022;13(5): 365–366. <https://doi.org/10.1136/flgastro-2022-102136>.
66. Sivananthan A, Glover B, Patel K, Ayaru L, Darzi A, Patel N. The evolution of lower gastrointestinal endoscopy; where are we now. *Therapeutic Advances in Gastrointestinal Endoscopy*. 2020; <https://doi.org/10.1177/2631774520979591>.
67. Harlow C, Sivananthan A, Ayaru L, Patel K, Darzi A, Patel N. Endoscopic submucosal dissection: an update on tools and accessories. *Therapeutic Advances in Gastrointestinal Endoscopy*. 2020;13: 1–13. <https://doi.org/10.1177/2631774520957220>.
68. Hassan C, Spadaccini M, Iannone A, Maselli R, Jovani M, Chandrasekar VT, et al. Performance of artificial intelligence in colonoscopy for adenoma and polyp detection: a systematic review and meta-analysis. *Gastrointestinal Endoscopy*. 2020; <https://doi.org/10.1016/j.gie.2020.06.059>.
69. Barua I, Vinsard DG, Jodal HC, Løberg M, Kalager M, Holme Ø, et al. Artificial intelligence for polyp detection during colonoscopy: a systematic review and meta-analysis. *Endoscopy*. 2020; <https://doi.org/10.1055/a-1201-7165>.

70. Nazarian S, Glover B, Ashrafian H, Darzi A, Teare J. Diagnostic Accuracy of Artificial Intelligence and Computer-Aided Diagnosis for the Detection and Characterization of Colorectal Polyps: Systematic Review and Meta-analysis. *Journal of medical Internet research*. 2021;23(7): e27370. <https://doi.org/10.2196/27370>.
71. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*. 2009;6(7). <https://doi.org/10.1371/journal.pmed.1000097>.
72. Joshi P, Stark K, Kumar A, Vidyarthi G, Medicine B, Ghavimi S, et al. Introduction: Adenoma detection rate (ADR) is a widely used quality indicator (QI) of colonoscopy. 2016;111(OCTOBER): 90–91.
73. Delavari A, Salimzadeh H, Bishehsari F, Sobh Rakhshankhah E, Delavari F, Moossavi S, et al. Mean Polyp per Patient Is an Accurate and Readily Obtainable Surrogate for Adenoma Detection Rate: Results from an Opportunistic Screening Colonoscopy Program. *Middle East journal of digestive diseases*. 2015;7(4): 214–219.
74. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Controlled Clinical Trials*. 1996;17(1): 1–12. [https://doi.org/10.1016/0197-2456\(95\)00134-4](https://doi.org/10.1016/0197-2456(95)00134-4).
75. Y. L, Y. Z, M. L, Y. L, P. L, Z. W, et al. Artificial Intelligence-Assisted Colonoscopy for Detection of Colon Polyps: a Prospective, Randomized Cohort Study. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract*. 2020; <http://dx.doi.org/10.1007/s11605-020-04802-4>.
76. Wang P, Berzin TM, Glissen Brown JR, Bharadwaj S, Becq A, Xiao X, et al. Real-time automatic detection system increases colonoscopic polyp and adenoma detection rates: a prospective randomised controlled study. *Gut*. 2019; <https://doi.org/10.1136/gutjnl-2018-317500>.
77. Wang P, Liu X, Berzin TM, Glissen Brown JR, Liu P, Zhou C, 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;0(0). [https://doi.org/10.1016/s2468-1253\(19\)30411-x](https://doi.org/10.1016/s2468-1253(19)30411-x).
78. Su JR, Li Z, Shao XJ, Ji CR, Ji R, Zhou RC, et al. Impact of a real-time automatic quality control system on colorectal polyp and adenoma detection: a prospective randomized controlled study (with videos). *Gastrointestinal endoscopy*. 2020;91(2): 415-424.e4. <https://dx.doi.org/10.1016/j.gie.2019.08.026>.
79. D. G, L. W, J. Z, G. M, L. S, J. L, et al. Detection of colorectal adenomas with a real-time computer-aided system (ENDOANGEL): a randomised controlled study. *The Lancet Gastroenterology and Hepatology*. 2020;5(4): 352–361. <http://dx.doi.org/10.1016/S2468-1253%2819%2930413-3>.
80. Liu WN, Zhang YY, Bian XQ, Wang LJ, Yang Q, Zhang XD, et al. Study on detection rate of polyps and adenomas in artificial-intelligence-aided colonoscopy. *Saudi journal of*

gastroenterology : official journal of the Saudi Gastroenterology Association. 2020;26(1): 13–19. https://dx.doi.org/10.4103/sjg.SJG_377_19.

81. Repici A, Badalamenti M, Maselli R, Correale L, Radaelli F, Rondonotti E, et al. Efficacy of Real-Time Computer-Aided Detection of Colorectal Neoplasia in a Randomized Trial. *Gastroenterology*. 2020;159(2): 512-520.e7. <https://doi.org/10.1053/j.gastro.2020.04.062>.
82. Zachariah R, Samarasena J, Luba D, Duh E, Dao T, Requa J, et al. Prediction of Polyp Pathology Using Convolutional Neural Networks Achieves ‘resect and Discard’ Thresholds. *American Journal of Gastroenterology*. 2020;115(1): 138–144. <https://doi.org/10.14309/ajg.0000000000000429>.
83. E. RD, G. B. Development of computer-assisted real time histology of colorectal polyps based on the nice criteria using nearfocus narrow-band imaging. *Gastroenterology*. 2017;152(5 Supplement 1): S81.
84. James P, Hegagi M, Hegagi M, Antonova L, Rostom A, Dube C, et al. Variable Endoscopist performance in proximal and distal adenoma detection during colonoscopy: A retrospective cohort study. *BMC Gastroenterology*. 2018;18(1): 73. <https://doi.org/10.1186/s12876-018-0800-4>.
85. Vleugels JLA, Hassan C, Senore C, Cassoni P, Baron JA, Rex DK, et al. Diminutive Polyps With Advanced Histologic Features Do Not Increase Risk for Metachronous Advanced Colon Neoplasia. *Gastroenterology*. 2019;156(3): 623-634.e3. <https://doi.org/10.1053/j.gastro.2018.10.050>.
86. Kim JY, Kim TJ, Baek SY, Ahn S, Kim ER, Hong SN, et al. Risk of Metachronous Advanced Neoplasia in Patients With Multiple Diminutive Adenomas. *American Journal of Gastroenterology*. 2018;(June): 1855–1861. <https://doi.org/10.1038/s41395-018-0210-9>.
87. Sivananthan A, Kerry G, Darzi A, Patel K, Patel N. Orientation in upper gastrointestinal endoscopy-the only way is up. *World Journal of Gastrointestinal Endoscopy*. 2023;15(3): 146–152. <https://doi.org/10.4253/wjge.v15.i3.146>.
88. *Product Features - SCOPEPILOT*. <http://www.scopepilot.com/product-features.html> [Accessed 8th January 2024].
89. Menon S, Trudgill N. How commonly is upper gastrointestinal cancer missed at endoscopy? A meta-analysis. *Endoscopy international open*. 2014;2(2): E46-50. <https://doi.org/10.1055/s-0034-1365524>.
90. Beg S, Ragunath K, Wyman A, Banks M, Trudgill N, Pritchard MD, et al. Quality standards in upper gastrointestinal endoscopy: a position statement of the British Society of Gastroenterology (BSG) and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS). *Gut*. 2017;66(11): 1886–1899. <https://doi.org/10.1136/gutjnl-2017-314109>.
91. Emura F, Gomez-Esquivel R, Rodriguez-Reyes C, Benias P, Preciado J, Wallace M, et al. Endoscopic identification of endoluminal esophageal landmarks for radial and

longitudinal orientation and lesion location. *World journal of gastroenterology*. 2019;25(4): 498–508. <https://doi.org/10.3748/wjg.v25.i4.498>.

92. Emura F, Sharma P, Arantes V, Cerisoli C, Parra-Blanco A, Sumiyama K, et al. Principles and practice to facilitate complete photodocumentation of the upper gastrointestinal tract: World Endoscopy Organization position statement. *Digestive Endoscopy*. 2020;32(2): 168–179. <https://doi.org/10.1111/den.13530>.
93. Cassaro M, Rugge M, Gutierrez O, Leandro G, Graham DY, Genta RM. Topographic patterns of intestinal metaplasia and gastric cancer. *The American journal of gastroenterology*. 2000;95(6): 1431–1438. <https://doi.org/10.1111/j.1572-0241.2000.02074.x>.
94. Bertleff MJOE, Lange JF. Perforated Peptic Ulcer Disease: A Review of History and Treatment. *Digestive Surgery*. 2010;27(3): 161–169. <https://doi.org/10.1159/000264653>.
95. Hennessy E. Perforated Peptic Ulcer: Mortality and Morbidity in 603 Cases. *The Australian and New Zealand Journal of Surgery*. 1972;38(3): 243–252. <https://doi.org/10.1111/j.1445-2197.1972.tb05628.x>.
96. Mille M, Engelhardt T, Stier A. Bleeding Duodenal Ulcer: Strategies in High-Risk Ulcers. *Visceral Medicine*. 2021;37(1): 52–62. <https://doi.org/10.1159/000513689>.
97. Elmunzer BJ, Young SD, Inadomi JM, Schoenfeld P, Laine L. Systematic Review of the Predictors of Recurrent Hemorrhage After Endoscopic Hemostatic Therapy for Bleeding Peptic Ulcers. *The American Journal of Gastroenterology*. 2008;103(10): 2625–2632. <https://doi.org/10.1111/j.1572-0241.2008.02070.x>.
98. Straker J C; Nord H J RJB. Endoscopic Orientation within the Duodenal Bulb. *Endoscopy*. 1992;24(04): 266–267. <https://doi.org/10.1055/s-2007-1010478>.
99. Salmon PR, Brown P, Htut T, Read AE. Endoscopic examination of the duodenal bulb: clinical evaluation of forward- and side-viewing fiberoptic systems in 200 cases. *Gut*. 1972;13(3): 170–175. <https://doi.org/10.1136/gut.13.3.170>.
100. Januszewicz W, Kaminski MF. Quality indicators in diagnostic upper gastrointestinal endoscopy. *Therapeutic Advances in Gastroenterology*. 2020;13: 175628482091669. <https://doi.org/10.1177/1756284820916693>.
101. Canard JM, Létard JC, Lennon AM. Diagnostic upper endoscopy. In: *Gastrointestinal Endoscopy in Practice*. Elsevier; 2011. p. 84–100. <https://doi.org/10.1016/B978-0-7020-3128-1.00003-1>. [Accessed 8th January 2024].
102. Lee SH, Park YK, Cho SM, Kang JK, Lee DJ. Technical skills and training of upper gastrointestinal endoscopy for new beginners. *World Journal of Gastroenterology*. 2015;21(3): 759. <https://doi.org/10.3748/wjg.v21.i3.759>.
103. *Centra Disposable Biopsy Forceps | STERIS*. <https://www.steris.com/healthcare/products/endoscopy-devices/polypectomy-and->

tissue-acquisition-devices/centra-disposable-biopsy-forceps# [Accessed 10th January 2024].

104. Barkun A, Liu J, Carpenter S, Chotiprasidhi P, Chuttani R, Ginsberg G, et al. Update on endoscopic tissue sampling devices. *Gastrointestinal Endoscopy*. 2006;63(6): 741–745. <https://doi.org/10.1016/j.gie.2006.02.041>.
105. Faigel DO, Eisen GM, Baron TH, Dominitz JA, Goldstein JL, Hirota WK, et al. Tissue sampling and analysis. *Gastrointestinal Endoscopy*. 2003;57(7): 811–816. [https://doi.org/10.1016/S0016-5107\(03\)70047-9](https://doi.org/10.1016/S0016-5107(03)70047-9).
106. Gilbert DA, DiMarino AJ, Jensen DM, Katon R, Kimmey MB, Laine LA, et al. Status evaluation: hot biopsy forceps. American Society for Gastrointestinal Endoscopy. Technology Assessment Committee. *Gastrointestinal Endoscopy*. 1992;38(6): 753–756.
107. Kaltenbach T, Anderson JC, Burke CA, Dominitz JA, Gupta S, Lieberman D, et al. Endoscopic Removal of Colorectal Lesions—Recommendations by the US Multi-Society Task Force on Colorectal Cancer. *Gastrointestinal Endoscopy*. 2020;91(3): 486–519. <https://doi.org/10.1016/j.gie.2020.01.029>.
108. Ellis K, Schiele M, Marquis S, Katon R. Efficacy of hot biopsy forceps. Cold micro-snare and micro-snare with cautery techniques in the removal of diminutive colonic polyps. *Gastrointestinal Endoscopy*. 1997;45(4): AB107. [https://doi.org/10.1016/S0016-5107\(97\)80330-6](https://doi.org/10.1016/S0016-5107(97)80330-6).
109. Fyock CJ, Draganov PV. Colonoscopic polypectomy and associated techniques. *World Journal of Gastroenterology*. 2010;16(29): 3630–3637. <https://doi.org/10.3748/wjg.v16.i29.3630>.
110. Peluso F, Goldner F. Follow-up of hot biopsy forceps treatment of diminutive colonic polyps. *Gastrointestinal Endoscopy*. 1991;37(6): 604–606. [https://doi.org/10.1016/S0016-5107\(91\)70863-8](https://doi.org/10.1016/S0016-5107(91)70863-8).
111. Raad D, Tripathi P, Cooper G, Falck-Ytter Y. Role of the cold biopsy technique in diminutive and small colonic polyp removal: a systematic review and meta-analysis. *Gastrointestinal Endoscopy*. 2016;83(3): 508–515. <https://doi.org/10.1016/j.gie.2015.10.038>.
112. *Local recurrence of diminutive colorectal polyps after cold forceps polypectomy with jumbo forceps followed by magnified narrow-band imaging: a multicenter prospective study - PubMed*. <https://pubmed.ncbi.nlm.nih.gov/30674046/> [Accessed 10th January 2024].
113. Park HJ. Endoscopic Instruments and Electrosurgical Unit for Colonoscopic Polypectomy. *Clinical Endoscopy*. 2016;49(4): 350–354. <https://doi.org/10.5946/ce.2016.059>.
114. Shinozaki S, Kobayashi Y, Hayashi Y, Sakamoto H, Lefor AK, Yamamoto H. Efficacy and safety of cold versus hot snare polypectomy for resecting small colorectal polyps: Systematic review and meta-analysis. *Digestive Endoscopy*. 2018;30(5): 592–599. <https://doi.org/10.1111/den.13173>.

115. Qu J, Jian H, Li L, Zhang Y, Feng B, Li Z, et al. Effectiveness and safety of cold versus hot snare polypectomy: A meta-analysis. *Journal of Gastroenterology and Hepatology*. 2019;34(1): 49–58. <https://doi.org/10.1111/jgh.14464>.
116. Yamashina T, Fukuhara M, Maruo T, Tanke G, Marui S, Sada R, et al. Cold snare polypectomy reduced delayed postpolypectomy bleeding compared with conventional hot polypectomy: a propensity score-matching analysis. *Endoscopy International Open*. 2017;05(7): E587–E594. <https://doi.org/10.1055/s-0043-105578>.
117. Chang LC, Shun CT, Hsu WF, Tu CH, Chen CC, Wu MS, et al. Risk of delayed bleeding before and after implementation of cold snare polypectomy in a screening colonoscopy setting. *Endoscopy International Open*. 2019;07(2): E232–E238. <https://doi.org/10.1055/a-0810-0439>.
118. Arimoto J, Chiba H, Ashikari K, Fukui R, Anan H, Tachikawa J, et al. Safety of Cold Snare Polypectomy in Patients Receiving Treatment with Antithrombotic Agents. *Digestive Diseases and Sciences*. 2019;64(11): 3247–3255. <https://doi.org/10.1007/s10620-019-5469-1>.
119. Horiuchi A, Hosoi K, Kajiyama M, Tanaka N, Sano K, Graham DY. Prospective, randomized comparison of 2 methods of cold snare polypectomy for small colorectal polyps. *Gastrointestinal Endoscopy*. 2015;82(4): 686–692. <https://doi.org/10.1016/j.gie.2015.02.012>.
120. Makino T, Horiuchi A, Kajiyama M, Tanaka N, Sano K, Maetani I. Delayed Bleeding Following Cold Snare Polypectomy for Small Colorectal Polyps in Patients Taking Antithrombotic Agents. *Journal of Clinical Gastroenterology*. 2018;52(6): 502. <https://doi.org/10.1097/MCG.0000000000000802>.
121. Suzuki S, Gotoda T, Kusano C, Ikehara H, Sugita A, Yamauchi M, et al. Width and depth of resection for small colorectal polyps: hot versus cold snare polypectomy. *Gastrointestinal Endoscopy*. 2018;87(4): 1095–1103. <https://doi.org/10.1016/j.gie.2017.10.041>.
122. Ito A, Suga T, Ota H, Tateiwa N, Matsumoto A, Tanaka E. Resection depth and layer of cold snare polypectomy versus endoscopic mucosal resection. *Journal of Gastroenterology*. 2018;53(11): 1171–1178. <https://doi.org/10.1007/s00535-018-1446-2>.
123. Herman T, Megna B, Pallav K, Bilal M. Endoscopic mucosal resection: tips and tricks for gastrointestinal trainees. *Translational Gastroenterology and Hepatology*. 2023;8(0). <https://doi.org/10.21037/tgh-23-23>.
124. Thiruvengadam S, Fung B, Barakat M, Tabibian J. Endoscopic Mucosal Resection: Best Practices for Gastrointestinal Endoscopists. *Gastroenterology & hepatology*. 2022;18: 133–144.
125. Klein A, Bourke MJ. How to Perform High-Quality Endoscopic Mucosal Resection During Colonoscopy. *Gastroenterology*. 2017;152(3): 466–471. <https://doi.org/10.1053/j.gastro.2016.12.029>.

126. Chandrasekar VT, Spadaccini M, Aziz M, Maselli R, Hassan S, Fuccio L, et al. Cold snare endoscopic resection of nonpedunculated colorectal polyps larger than 10 mm: a systematic review and pooled-analysis. *Gastrointestinal Endoscopy*. 2019;89(5): 929-936.e3. <https://doi.org/10.1016/j.gie.2018.12.022>.
127. Tutticci NJ, Kheir AO, Hewett DG. The Cold Revolution: How Far Can It Go? *Gastrointestinal Endoscopy Clinics of North America*. 2019;29(4): 721–736. <https://doi.org/10.1016/j.giec.2019.06.003>.
128. Choi AY, Moosvi Z, Shah S, Roccato MK, Wang AY, Hamerski CM, et al. Underwater versus conventional EMR for colorectal polyps: systematic review and meta-analysis. *Gastrointestinal Endoscopy*. 2021;93(2): 378–389. <https://doi.org/10.1016/j.gie.2020.10.009>.
129. Asano M. Endoscopic submucosal dissection and surgical treatment for gastrointestinal cancer. *World Journal of Gastrointestinal Endoscopy*. 2012;4(10): 438–447. <https://doi.org/10.4253/wjge.v4.i10.438>.
130. Fukuzawa M, Gotoda T. History of endoscopic submucosal dissection and role for colorectal endoscopic submucosal dissection: A Japanese perspective. *Gastrointestinal Intervention*. 2012;1(1): 30–35. <https://doi.org/10.1016/j.gii.2012.09.001>.
131. Patel N, Patel K, Ashrafian H, Athanasiou T, Darzi A, Teare J. Colorectal endoscopic submucosal dissection: Systematic review of mid-term clinical outcomes. *Digestive Endoscopy*. 2016;28(4): 405–416. <https://doi.org/10.1111/den.12597>.
132. Wang J, Zhang XH, Ge J, Yang CM, Liu JY, Zhao SL. Endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal tumors: a meta-analysis. *World journal of gastroenterology*. 2014;20(25): 8282–8287. <https://doi.org/10.3748/wjg.v20.i25.8282>.
133. Fuccio L, Hassan C, Ponchon T, Mandolesi D, Farioli A, Cucchetti A, et al. Clinical outcomes after endoscopic submucosal dissection for colorectal neoplasia: a systematic review and meta-analysis. *Gastrointestinal Endoscopy*. 2017;86(1): 74-86.e17. <https://doi.org/10.1016/j.gie.2017.02.024>.
134. Okamoto K, Muguruma N, Kagemoto K, Mitsui Y, Fujimoto D, Kitamura S, et al. Efficacy of hybrid endoscopic submucosal dissection (ESD) as a rescue treatment in difficult colorectal ESD cases. *Digestive Endoscopy: Official Journal of the Japan Gastroenterological Endoscopy Society*. 2017;29 Suppl 2: 45–52. <https://doi.org/10.1111/den.12863>.
135. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, De Ceglie A, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*. 2015;47(9): 829–854. <https://doi.org/10.1055/s-0034-1392882>.
136. Choi HS, Chun HJ. Accessory devices frequently used for endoscopic submucosal dissection. *Clinical Endoscopy*. 2017;50(3): 224–233. <https://doi.org/10.5946/ce.2017.070>.

137. Odagiri H, Yasunaga H. Complications following endoscopic submucosal dissection for gastric, esophageal, and colorectal cancer: a review of studies based on nationwide large-scale databases. *Annals of translational medicine*. 2017;5(8): 189.
<https://doi.org/10.21037/atm.2017.02.12>.
138. Kuwai T, Yamaguchi T, Imagawa H, Miura R, Sumida Y, Takasago T, et al. Endoscopic submucosal dissection for early esophageal neoplasms using the stag beetle knife. *World Journal of Gastroenterology*. 2018;24(15): 1632–1640.
<https://doi.org/10.3748/wjg.v24.i15.1632>.
139. Homma K, Kobayashi M. Endoscopic Submucosal Dissection with a Scissor-Type Knife: Selection of the Appropriate Sb Knife and Tips for Manipulation According to Each Situation (with Videos). *Gastroenterological Endoscopy*. 2021;63(6): 1281–1293.
<https://doi.org/10.11280/gee.63.1281>.
140. Homma K, Otaki Y, Sugawara M, Kobayashi M. Efficacy of novel SB knife Jr examined in a multicenter study on colorectal endoscopic submucosal dissection. *Digestive Endoscopy: Official Journal of the Japan Gastroenterological Endoscopy Society*. 2012;24 Suppl 1: 117–120. <https://doi.org/10.1111/j.1443-1661.2012.01266.x>.
141. Oka S, Tanaka S, Takata S, Kanao H, Chayama K. Usefulness and safety of SB knife Jr in endoscopic submucosal dissection for colorectal tumors. *Digestive Endoscopy: Official Journal of the Japan Gastroenterological Endoscopy Society*. 2012;24 Suppl 1: 90–95.
<https://doi.org/10.1111/j.1443-1661.2012.01255.x>.
142. Sawas T, Visrodia KH, Zakko L, Lutzke LS, Leggett CL, Wang KK. Clutch cutter is a safe device for performing endoscopic submucosal dissection of superficial esophageal neoplasms: a western experience. *Diseases of the Esophagus: Official Journal of the International Society for Diseases of the Esophagus*. 2018;31(11).
<https://doi.org/10.1093/dote/doy054>.
143. Hayashi Y, Esaki M, Suzuki S, Ihara E, Yokoyama A, Sakisaka S, et al. Clutch Cutter knife efficacy in endoscopic submucosal dissection for early gastric neoplasms. *World Journal of Gastrointestinal Oncology*. 2018;10(12): 487–495.
<https://doi.org/10.4251/wjgo.v10.i12.487>.
144. Toyonaga T, Man-I M, Fujita T, Nishino E, Ono W, Morita Y, et al. The performance of a novel ball-tipped Flush knife for endoscopic submucosal dissection: a case-control study. *Alimentary Pharmacology & Therapeutics*. 2010;32(7): 908–915.
<https://doi.org/10.1111/j.1365-2036.2010.04425.x>.
145. Toyonaga T, Man-i M, Fujita T, East JE, Coumaros D, Morita Y, et al. Endoscopic submucosal dissection using the Flush knife and the Flush knife BT. *Techniques in Gastrointestinal Endoscopy*. 2011;13(1): 84–90.
<https://doi.org/10.1016/j.tgie.2011.02.003>.
146. Takeuchi Y, Uedo N, Ishihara R, Iishi H, Kizu T, Inoue T, et al. Efficacy of an endo-knife with a water-jet function (Flushknife) for endoscopic submucosal dissection of superficial

colorectal neoplasms. *The American Journal of Gastroenterology*. 2010;105(2): 314–322. <https://doi.org/10.1038/ajg.2009.547>.

147. Liu Z, Zhang X, Guo X, Wu K. Sa1393 O-Type Hybrid Knife Shortens the Dissection Time of Gastric Endoscopic Submucosal Dissection in a Pilot Perspective Trial. *Gastrointestinal Endoscopy*. 2013;77: AB189. <https://doi.org/10.1016/j.gie.2013.03.444>.
148. Zhou PH, Schumacher B, Yao LQ, Xu MD, Nordmann T, Cai MY, et al. Conventional vs. waterjet-assisted endoscopic submucosal dissection in early gastric cancer: a randomized controlled trial. *Endoscopy*. 2014;46(10): 836–843. <https://doi.org/10.1055/s-0034-1377580>.
149. Huang R, Yan H, Ren G, Pan Y, Zhang L, Liu Z, et al. Comparison of O-Type Hybrid Knife to Conventional Knife in Endoscopic Submucosal Dissection for Gastric Mucosal Lesions. *Medicine*. 2016;95(13): e3148. <https://doi.org/10.1097/MD.0000000000003148>.
150. Akutsu D, Suzuki H, Narasaka T, Terasaki M, Kaneko T, Matsui H, et al. The effectiveness of gastric endoscopic submucosal dissection using hybridknife® with the erbejet 2 system. *Gastroenterological Endoscopy*. 2017;59: 2621–2627.
151. Kanzaki H, Ishihara R, Ohta T, Nagai K, Matsui F, Yamashina T, et al. Randomized study of two endo-knives for endoscopic submucosal dissection of esophageal cancer. *The American Journal of Gastroenterology*. 2013;108(8): 1293–1298. <https://doi.org/10.1038/ajg.2013.161>.
152. De-la-Peña J, Calderón Á, Esteban JM, López-Rosés L, Martínez-Ares D, Nogales Ó, et al. Experimental study of hybrid-knife endoscopic submucosal dissection (ESD) versus standard ESD in a Western country. *Revista Espanola De Enfermedades Digestivas*. 2014;106(2): 98–102. <https://doi.org/10.4321/s1130-01082014000200005>.
153. Suzuki T, Hara T, Kitagawa Y, Yamaguchi T. Usefulness of IT knife nano for endoscopic submucosal dissection of large colo-rectal lesions. *Acta Gastro-Enterologica Belgica*. 2016;79(2): 186–190.
154. jRCT1042180137. A randomized control trial of efficacy of endoscopic submucosal dissection using an ITknife nano for colorectal neoplasms larger than 30 mm in size. <https://trialsearch.who.int/Trial2.aspx?TrialID=JPRN-jRCT1042180137>. 2019; <https://doi.org/10.1002/central/CN-01971805>.
155. Kim HG, Cho JY, Bok GH, Cho WY, Kim WJ, Hong SJ, et al. A novel device for endoscopic submucosal dissection, the Fork knife. *World Journal of Gastroenterology : WJG*. 2008;14(43): 6726–6732. <https://doi.org/10.3748/wjg.14.6726>.
156. Fujinami H, Hosokawa A, Ogawa K, Nishikawa J, Kajiura S, Ando T, et al. Endoscopic submucosal dissection for superficial esophageal neoplasms using the stag beetle knife. *Diseases of the Esophagus: Official Journal of the International Society for Diseases of the Esophagus*. 2014;27(1): 50–54. <https://doi.org/10.1111/dote.12039>.

157. Chung WC, Kim BW, Lim CH, Kim TH, Park JM, Kim JS. Grasper type scissors for endoscopic submucosal dissection of gastric epithelial neoplasia. *World Journal of Gastroenterology : WJG*. 2013;19(37): 6221–6227. <https://doi.org/10.3748/wjg.v19.i37.6221>.
158. Visrodia K, Sawas T, Zakko L, Genere JR, Leggett C, Lutzke L, et al. Scissor-type knife improves the safety of endoscopic submucosal dissection (ESD) among endoscopists without experience in ESD: a randomized ex vivo study. *Endoscopy International Open*. 2021;9(8): E1207–E1213. <https://doi.org/10.1055/a-1487-5469>.
159. Yamashina T, Takeuchi Y, Nagai K, Matsuura N, Ito T, Fujii M, et al. Scissor-type knife significantly improves self-completion rate of colorectal endoscopic submucosal dissection: Single-center prospective randomized trial. *Digestive Endoscopy: Official Journal of the Japan Gastroenterological Endoscopy Society*. 2017;29(3): 322–329. <https://doi.org/10.1111/den.12784>.
160. Esaki M, Hayashi Y, Ikehara H, Ihara E, Horii T, Tamura Y, et al. The effect of scissor-type versus non-scissor-type knives on the technical outcomes in endoscopic submucosal dissection for superficial esophageal cancer: a multi-center retrospective study. *Diseases of the Esophagus: Official Journal of the International Society for Diseases of the Esophagus*. 2020;33(4): doz077. <https://doi.org/10.1093/dote/doz077>.
161. Yachida T, Kobara H, Kozuka K, Nakatani K, Tada N, Matsui T, et al. Comparison of Needle Knife versus Scissors Forceps for Colorectal Endoscopic Submucosal Dissection: A Prospective Randomized Study. *Journal of Clinical Medicine*. 2023;12(6): 2329. <https://doi.org/10.3390/jcm12062329>.
162. Nagai K, Uedo N, Yamashina T, Matsui F, Matsuura N, Ito T, et al. A comparative study of grasping-type scissors forceps and insulated-tip knife for endoscopic submucosal dissection of early gastric cancer: a randomized controlled trial. *Endoscopy International Open*. 2016;4(6): E654–E660. <https://doi.org/10.1055/s-0042-105870>.
163. Sugihara Y, Harada K, Kawahara Y, Takei D, Takashima S, Inokuchi T, et al. Two electrosurgical endo-knives for endoscopic submucosal dissection of colorectal superficial neoplasms: a prospective randomized study. *Endoscopy International Open*. 2017;5(8): E729–E735. <https://doi.org/10.1055/s-0043-111792>.
164. Lim TW, Ryu DG, Kim WC, Nam HS, Kang DH, Kim HW, et al. Sa1611 Endoscopic Mucosal Resection With CAP Demonstrates a Superior Rate of Histologic Complete Resection Over Endoscopic Submucosal Dissection for Rectal Neuroendocrine Tumors. *Gastrointestinal Endoscopy*. 2015;81(5): AB282. <https://doi.org/10.1016/j.gie.2015.03.1400>.
165. Yang DH, Park Y, Park SH, Kim KJ, Ye BD, Byeon JS, et al. Cap-assisted EMR for rectal neuroendocrine tumors: comparisons with conventional EMR and endoscopic submucosal dissection (with videos). *Gastrointestinal Endoscopy*. 2016;83(5): 1015–1022; quiz 1023-.e6. <https://doi.org/10.1016/j.gie.2015.09.046>.

166. Yamamoto H, Kawata H, Sunada K, Sasaki A, Nakazawa K, Miyata T, et al. Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. *Endoscopy*. 2003;35(8): 690–694. <https://doi.org/10.1055/s-2003-41516>.
167. Liu CY, Chen PJ, Chen CC, Lee CT, Lee IL, Hsu WH, et al. Sa1597 ENDOLIFTER Shortens the Submucosal Dissection Time of Gastric Endoscopic Submucosal Dissection With Better Safety in Live Porcine Model. *Gastrointestinal Endoscopy*. 2012;75(4): AB214–AB215. <https://doi.org/10.1016/j.gie.2012.04.386>.
168. Jy J. Future Development of Endoscopic Accessories for Endoscopic Submucosal Dissection. *Clinical endoscopy*. 2017;50(3). <https://doi.org/10.5946/ce.2017.073>.
169. Jung YS, Park and DI. Submucosal injection solutions for endoscopic mucosal resection and endoscopic submucosal dissection of gastrointestinal neoplasms. *International Journal of Gastrointestinal Intervention*. 2013;2(2): 73–77. <https://doi.org/10.1016/j.gii.2013.09.003>.
170. M F, N Y, K K, T M, M N, N K, et al. Tissue damage of different submucosal injection solutions for EMR. *Gastrointestinal endoscopy*. 2005;62(6). <https://doi.org/10.1016/j.gie.2005.07.052>.
171. Ab F, Cj G, Lj B, A B, Lj H, E R. Hydroxypropyl methylcellulose: A better submucosal fluid cushion for endoscopic mucosal resection. *Gastrointestinal endoscopy*. 2003;57(1). <https://doi.org/10.1067/mge.2003.25>.
172. J J, S K, P C, Cy C, M DG, T T, et al. HybridKnife high-pressure glycerol jet injection for endoscopic submucosal dissection increases procedural ease and speed: a randomised study in pigs and a human case series. *Surgical endoscopy*. 2016;30(7). <https://doi.org/10.1007/s00464-015-4554-6>.
173. Yamamoto H, Yahagi N, Oyama T, Gotoda T, Doi T, Hirasaki S, et al. Usefulness and safety of 0.4% sodium hyaluronate solution as a submucosal fluid ‘cushion’ in endoscopic resection for gastric neoplasms: a prospective multicenter trial. *Gastrointestinal endoscopy*. 2008;67(6): 830–839. <https://doi.org/10.1016/j.gie.2007.07.039>.
174. Yamamoto H, Kawata H, Sunada K, Satoh K, Kaneko Y, Ido K, et al. Success rate of curative endoscopic mucosal resection with circumferential mucosal incision assisted by submucosal injection of sodium hyaluronate. *Gastrointestinal Endoscopy*. 2002;56(4): 507–512. <https://doi.org/10.1067/mge.2002.128108>.
175. Matsui Y, Inomata M, Izumi K, Sonoda K, Shiraishi N, Kitano S. Hyaluronic acid stimulates tumor-cell proliferation at wound sites. *Gastrointestinal Endoscopy*. 2004;60(4): 539–543. [https://doi.org/10.1016/s0016-5107\(04\)01890-5](https://doi.org/10.1016/s0016-5107(04)01890-5).
176. Uemura N, Oda I, Saito Y, Ono H, Fujisaki J, Matsuhashi N, et al. Efficacy and safety of 0.6% sodium alginate solution in endoscopic submucosal dissection for esophageal and gastric neoplastic lesion: A randomized controlled study. *Digestive Endoscopy: Official*

Journal of the Japan Gastroenterological Endoscopy Society. 2019;31(4): 396–404.
<https://doi.org/10.1111/den.13352>.

177. Repici A, Wallace M, Sharma P, Bhandari P, Lollo G, Maselli R, et al. A novel submucosal injection solution for endoscopic resection of large colorectal lesions: a randomized, double-blind trial. *Gastrointestinal endoscopy*. 2018;88(3): 527-535.e5.
<https://doi.org/10.1016/j.gie.2018.04.2363>.
178. Mehta N, Strong AT, Franco M, Stevens T, Chahal P, Jang S, et al. Optimal injection solution for endoscopic submucosal dissection: A randomized controlled trial of Western solutions in a porcine model. *Digestive Endoscopy: Official Journal of the Japan Gastroenterological Endoscopy Society*. 2018;30(3): 347–353.
<https://doi.org/10.1111/den.12993>.
179. Huai ZY, Feng Xian W, Chang Jiang L, Xi Chen W. Submucosal injection solution for endoscopic resection in gastrointestinal tract: a traditional and network meta-analysis. *Gastroenterology Research and Practice*. 2015;2015: 702768.
<https://doi.org/10.1155/2015/702768>.
180. Esaki M, Suzuki S, Hayashi Y, Yokoyama A, Abe S, Hosokawa T, et al. Splash M-knife versus Flush Knife BT in the technical outcomes of endoscopic submucosal dissection for early gastric cancer: a propensity score matching analysis. *BMC gastroenterology*. 2018;18(1): 35. <https://doi.org/10.1186/s12876-018-0763-5>.
181. Nonaka S, Saito Y, Fukunaga S, Sakamoto T, Nakajima T, Matsuda T. Impact of endoscopic submucosal dissection knife on risk of perforation with an animal model-monopolar needle knife and with a bipolar needle knife. *Digestive Endoscopy: Official Journal of the Japan Gastroenterological Endoscopy Society*. 2012;24(5): 381.
<https://doi.org/10.1111/j.1443-1661.2012.01249.x>.
182. Harada A, Gotoda T, Fukuzawa M, Moriyasu F. Clinical impact of endoscopic devices for colorectal endoscopic submucosal dissection. *Digestion*. 2013;88(2): 72–78.
<https://doi.org/10.1159/000352024>.
183. Tsiamoulos ZP, Hancock CP, Polecina A, Sibbons PD, Saunders BP. Comparison of Bipolar Radiofrequency Cutting and Mono Polar Cutting for Endoscopic Submucosal Dissection (ESD) in a Porcine Model. *Gastrointestinal Endoscopy*. 2014;79(5): AB257.
<https://doi.org/10.1016/j.gie.2014.05.184>.
184. Kataoka M, Kawai T, Hayama Y, Yamamoto K, Nonaka M, Aoki T, et al. Comparison of hemostasis using bipolar hemostatic forceps with hemostasis by endoscopic hemoclippping for nonvariceal upper gastrointestinal bleeding in a prospective non-randomized trial. *Surgical Endoscopy*. 2013;27(8): 3035–3038.
<https://doi.org/10.1007/s00464-013-2860-4>.
185. Takizawa K, Oda I, Gotoda T, Yokoi C, Matsuda T, Saito Y, et al. Routine coagulation of visible vessels may prevent delayed bleeding after endoscopic submucosal dissection--an analysis of risk factors. *Endoscopy*. 2008;40(3): 179–183. <https://doi.org/10.1055/s-2007-995530>.

186. Azumi M, Takeuchi M, Koseki Y, Kumagai M, Kobayashi Y, Takatsuna M, et al. The search, coagulation, and clipping (SCC) method prevents delayed bleeding after gastric endoscopic submucosal dissection. *Gastric Cancer: Official Journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association*. 2019;22(3): 567–575. <https://doi.org/10.1007/s10120-018-0878-y>.
187. Hirasawa K, Sato C, Makazu M, Kaneko H, Kobayashi R, Kokawa A, et al. Coagulation syndrome: Delayed perforation after colorectal endoscopic treatments. *World Journal of Gastrointestinal Endoscopy*. 2015;7(12): 1055–1061. <https://doi.org/10.4253/wjge.v7.i12.1055>.
188. Zhang Y, Chen Y, Qu CY, Zhou M, Ni QW, Xu LM. Effects of medical adhesives in prevention of complications after endoscopic submucosal dissection. *World Journal of Gastroenterology*. 2013;19(17): 2704–2708. <https://doi.org/10.3748/wjg.v19.i17.2704>.
189. *Purastat® vs Standard Therapy for Haemostasis During Endoscopic Submucosal Dissection | Cochrane Library*. <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01584286/full?highlightAbstract=endoscopic%7Csubmucosal%7Cdissect%7Cwithdrawn%7Csubmucos%7Cendoscop%7Cdissection> [Accessed 11th January 2024].
190. Noguchi M, Yano T, Kato T, Kadota T, Imajoh M, Morimoto H, et al. Risk factors for intraoperative perforation during endoscopic submucosal dissection of superficial esophageal squamous cell carcinoma. *World Journal of Gastroenterology*. 2017;23(3): 478–485. <https://doi.org/10.3748/wjg.v23.i3.478>.
191. Akintoye E, Kumar N, Aihara H, Nas H, Thompson CC. Colorectal endoscopic submucosal dissection: a systematic review and meta-analysis. *Endoscopy International Open*. 2016;4(10): E1030–E1044. <https://doi.org/10.1055/s-0042-114774>.
192. Ding X, Luo H, Duan H. Risk factors for perforation of gastric endoscopic submucosal dissection: a systematic review and meta-analysis. *European Journal of Gastroenterology & Hepatology*. 2019;31(12): 1481–1488. <https://doi.org/10.1097/MEG.0000000000001543>.
193. Paspatis GA, Dumonceau JM, Barthet M, Meisner S, Repici A, Saunders BP, et al. Diagnosis and management of iatrogenic endoscopic perforations: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. *Endoscopy*. 2014;46(8): 693–711. <https://doi.org/10.1055/s-0034-1377531>.
194. Kim JS, Kim BW, Kim JI, Kim JH, Kim SW, Ji JS, et al. Endoscopic clip closure versus surgery for the treatment of iatrogenic colon perforations developed during diagnostic colonoscopy: a review of 115,285 patients. *Surgical Endoscopy*. 2013;27(2): 501–504. <https://doi.org/10.1007/s00464-012-2465-3>.
195. Kukreja K, Chennubhotla S, Bhandari B, Arora A, Singhal S. Closing the Gaps: Endoscopic Suturing for Large Submucosal and Full-Thickness Defects. *Clinical Endoscopy*. 2018;51(4): 352–356. <https://doi.org/10.5946/ce.2017.117>.

196. Tonai Y, Ishihara R, Yamasaki Y, Arao M, Iwatsubo T, Kato M, et al. Impact of electrosurgical unit mode on post esophageal endoscopic submucosal dissection stricture in an in vivo porcine model. *Endoscopy International Open*. 2018;6(3): E376–E381. <https://doi.org/10.1055/s-0043-122883>.
197. Xia M, Zhou Y, Yu J, Chen W, Huang X, Liao J. Short-term outcomes of traction-assisted versus conventional endoscopic submucosal dissection for superficial gastrointestinal neoplasms: a systematic review and meta-analysis of randomized controlled studies. *World Journal of Surgical Oncology*. 2019;17(1): 94. <https://doi.org/10.1186/s12957-019-1639-z>.
198. Jeon WJ, You IY, Chae HB, Park SM, Youn SJ. A new technique for gastric endoscopic submucosal dissection: peroral traction-assisted endoscopic submucosal dissection. *Gastrointestinal Endoscopy*. 2009;69(1): 29–33. <https://doi.org/10.1016/j.gie.2008.03.1126>.
199. Suzuki S, Gotoda T, Kobayashi Y, Kono S, Iwatsuka K, Yagi-Kuwata N, et al. Usefulness of a traction method using dental floss and a hemoclip for gastric endoscopic submucosal dissection: a propensity score matching analysis (with videos). *Gastrointestinal endoscopy*. 2016;83(2): 337–346. <https://doi.org/10.1016/j.gie.2015.07.014>.
200. Koike Y, Hirasawa D, Fujita N, Maeda Y, Ohira T, Harada Y, et al. Usefulness of the thread-traction method in esophageal endoscopic submucosal dissection: randomized controlled trial. *Digestive Endoscopy: Official Journal of the Japan Gastroenterological Endoscopy Society*. 2015;27(3): 303–309. <https://doi.org/10.1111/den.12396>.
201. Ritsuno H, Sakamoto N, Osada T, Goto SP, Murakami T, Ueyama H, et al. Prospective clinical trial of traction device-assisted endoscopic submucosal dissection of large superficial colorectal tumors using the S-O clip. *Surgical Endoscopy*. 2014;28(11): 3143–3149. <https://doi.org/10.1007/s00464-014-3572-0>.
202. Jacques J, Charissoux A, Legros R, Tailleux A, Rivory J, Albouis J, et al. Double-clip counter-traction using a rubber band is a useful and adaptive tool for colonic endoscopic submucosal dissection. *Endoscopy*. 2018;50(2): 179–181. <https://doi.org/10.1055/s-0043-122596>.
203. Imaeda H, Hosoe N, Ida Y, Kashiwagi K, Morohoshi Y, Suganuma K, et al. Novel technique of endoscopic submucosal dissection using an external grasping forceps for superficial gastric neoplasia. *Digestive Endoscopy: Official Journal of the Japan Gastroenterological Endoscopy Society*. 2009;21(2): 122–127. <https://doi.org/10.1111/j.1443-1661.2009.00842.x>.
204. Imaeda H, Hosoe N, Ida Y, Nakamizo H, Kashiwagi K, Kanai T, et al. Novel technique of endoscopic submucosal dissection by using external forceps for early rectal cancer (with videos). *Gastrointestinal Endoscopy*. 2012;75(6): 1253–1257. <https://doi.org/10.1016/j.gie.2012.02.018>.
205. Yoshida N, Doyama H, Ota R, Takeda Y, Nakanishi H, Tominaga K, et al. Effectiveness of clip-and-snare method using pre-looping technique for gastric endoscopic submucosal

dissection. *World Journal of Gastrointestinal Endoscopy*. 2016;8(12): 451–457. <https://doi.org/10.4253/wjge.v8.i12.451>.

206. Ota R, Doyama H, Tsuji K, Yamada S. Deep colonic endoscopic submucosal dissection using a modified clip and snare method incorporating a pre-looping technique. *BMJ case reports*. 2015;2015: bcr2014207918. <https://doi.org/10.1136/bcr-2014-207918>.
207. Uraoka T, Ishikawa S, Kato J, Higashi R, Suzuki H, Kaji E, et al. Advantages of using thin endoscope-assisted endoscopic submucosal dissection technique for large colorectal tumors. *Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society*. 2010;22(3): 186–191. <https://doi.org/10.1111/j.1443-1661.2010.00992.x>.
208. Jawaid S, Yang D, Draganov PV. Tissue retractor system-assisted endoscopic submucosal dissection of a large rectal tumor with significant fibrosis from direct tattooing. *VideoGIE: An Official Video Journal of the American Society for Gastrointestinal Endoscopy*. 2019;4(2): 84–86. <https://doi.org/10.1016/j.vgie.2018.10.008>.
209. Mortagy M, Mehta N, Parsi MA, Abe S, Stevens T, Vargo JJ, et al. Magnetic anchor guidance for endoscopic submucosal dissection and other endoscopic procedures. *World Journal of Gastroenterology*. 2017;23(16): 2883–2890. <https://doi.org/10.3748/wjg.v23.i16.2883>.
210. Barlow DE. How Endoscopes Work. In: Elsevier; 2012. p. 25–45. <https://doi.org/10.1016/B978-1-4377-1529-3.00003-8>. [Accessed 14th January 2024].
211. Kohli DR, Baillie J. 3 - How Endoscopes Work. In: Chandrasekhara V, Elmunzer BJ, Khashab MA, Muthusamy VR (eds.) *Clinical Gastrointestinal Endoscopy (Third Edition)*. Philadelphia: Elsevier; 2019. p. 24-31.e2. <https://doi.org/10.1016/B978-0-323-41509-5.00003-7>.
212. Soetikno R, Asokkumar R, Nguyen-Vu T, DeSimio T, Kaltenbach T. Holding and manipulating the endoscope: A user's guide. *Techniques in Gastrointestinal Endoscopy*. 2019;21(3): 124–132. <https://doi.org/10.1016/j.tgie.2019.07.006>.
213. Rozeboom E, Reilink R, Schwartz M, Fockens P, Broeders I. Evaluation of the tip-bending response in clinically used endoscopes. *Endoscopy International Open*. 2016;04(04): E466–E471. <https://doi.org/10.1055/s-0042-104115>.
214. Ranzani T, Russo S, Schwab F, Walsh C, Wood R. *Deployable stabilization mechanisms for endoscopic procedures*. 2017. <https://doi.org/10.1109/ICRA.2017.7989134>.
215. Khatait J. *Motion and Force Transmission of a Flexible Instrument Inside a Curved Endoscope*. 2013. <https://doi.org/10.3990/1.9789036500104>.
216. Khatait JP, Brouwer DM, Aarts RGKM, Herder JL. Modeling of a Flexible Instrument to Study its Sliding Behavior Inside a Curved Endoscope. *Journal of Computational and Nonlinear Dynamics*. 2012;8(031002). <https://doi.org/10.1115/1.4007539>.
217. Khatait JP, Brouwer DM, Soemers HMJR, Aarts RGKM, Herder JL. Design of an Experimental Set-Up to Study the Behavior of a Flexible Surgical Instrument Inside an

Endoscope. *Journal of Medical Devices*. 2013;7(031004).
<https://doi.org/10.1115/1.4024660>.

218. Khatait JP, Brouwer DM, Meijaard JP, Aarts RGKM, Herder JL. 3-D Multibody Modeling of a Flexible Surgical Instrument Inside an Endoscope. In: American Society of Mechanical Engineers Digital Collection; 2013. p. 271–280. <https://doi.org/10.1115/IMECE2012-87578>. [Accessed 13th January 2024].
219. Swain P, Sadaat V, Brenneman R, Ewers R. Force Transmission at Flexible Endoscopy with Conventional Endoscopes and Shape Locking Endoscope Guide Catheter. *Gastrointestinal Endoscopy*. 2004;59(5): P148. [https://doi.org/10.1016/S0016-5107\(04\)00711-4](https://doi.org/10.1016/S0016-5107(04)00711-4).
220. Swain P, Bally KR, Spivey JT, Bakos GJ, Stefanchik D. Controlled Comparison of Increased Force Transmission Delivered Via Five Novel Endoscope Stiffening Technologies. *Gastrointestinal Endoscopy*. 2008;67(5): AB115–AB116.
<https://doi.org/10.1016/j.gie.2008.03.1100>.
221. DeHaven KE. Principles of Triangulation for Arthroscopic Surgery. *Orthopedic Clinics of North America*. 1982;13(2): 329–336. [https://doi.org/10.1016/S0030-5898\(20\)30717-3](https://doi.org/10.1016/S0030-5898(20)30717-3).
222. Kotzampassi K, Grosomanidis V, Eleftheriadis E. Improving triangulation in notes by triple access. *Hellenic Journal of Surgery*. 2010;82(2): 95–100. <https://doi.org/10.1007/s13126-010-0014-x>.
223. Diana M, Chung H, Liu KH, Dallemagne B, Demartines N, Mutter D, et al. Endoluminal surgical triangulation: overcoming challenges of colonic endoscopic submucosal dissections using a novel flexible endoscopic surgical platform: feasibility study in a porcine model. *Surgical Endoscopy*. 2013;27(11): 4130–4135.
<https://doi.org/10.1007/s00464-013-3049-6>.
224. von Renteln D, Vassiliou MC, Rösch T, Rothstein RI. Triangulation: the holy grail of endoscopic surgery? *Surgical Endoscopy*. 2011;25(5): 1355–1357.
<https://doi.org/10.1007/s00464-011-1650-0>.
225. Rahman I, Boger P, Patel P. OC-012 The Effect of Mental Workload Experienced During Colonoscopy on Endoscopists Performance. *Gut*. 2016;65(Suppl 1): A9 LP-A9.
<https://doi.org/10.1136/gutjnl-2016-312388.12>.
226. Barbour JA, O'Toole P, Suzuki N, Dolwani S. Learning endoscopic submucosal dissection in the UK: Barriers, solutions and pathways for training. *Frontline Gastroenterology*. 2021;12(7): 671–676. <https://doi.org/10.1136/flgastro-2020-101526>.
227. Mans L, Arvanitakis M, Neuhaus H, Devière J. Motorized Spiral Enteroscopy for Occult Bleeding. *Digestive Diseases*. 2018;36(4): 325–327. <https://doi.org/10.1159/000488479>.
228. Morgan D, Upchurch B, Draganov P, Kenneth F, Haluszka O, Jonnalagadda S, et al. Spiral enteroscopy: prospective U.S. multicenter study in patients with small-bowel disorders. 2014;72(5): 992–998. <https://doi.org/10.1016/j.gie.2010.07.013.Spiral>.

229. Baniya R, Upadhaya S, Subedi SC, Khan J, Sharma P, Mohammed TS, et al. Balloon enteroscopy versus spiral enteroscopy for small-bowel disorders: a systematic review and meta-analysis. *Gastrointestinal Endoscopy*. 2017;86(6): 997–1005. <https://doi.org/10.1016/j.gie.2017.06.015>.
230. Beyna T, Schneider M, Pullmann D, Gerges C, Kandler J, Neuhaus H. Motorized spiral colonoscopy: A first single-center feasibility trial. *Endoscopy*. 2018;50(5): 518–523. <https://doi.org/10.1055/s-0043-123577>.
231. Beyna T, Arvanitakis M, Schneider M, Hoellerich J, Deviere J, Neuhaus H. First Prospective Clinical Trial on Total Motorized Spiral Enteroscopy (Tmset). *Gastrointestinal Endoscopy*. 2019;89(6): AB48. <https://doi.org/10.1016/j.gie.2019.04.002>.
232. Spada C, Hassan C, Cesaro P, Costamagna G. Spiraling your insertion: a glimpse into the future of colonoscopy. *Endoscopy*. 2018;50: 1469–1470. <https://doi.org/10.1136/gutjnl-2017-313905>.
233. Gluck N, Melhem A, Halpern Z, Mergener K, Santo E. A novel self-propelled disposable colonoscope is effective for colonoscopy in humans (with video). *Gastrointestinal Endoscopy*. 2016;83(5): 998–1004. <https://doi.org/10.1016/j.gie.2015.08.083>.
234. GI view. *FDA Aer-o-scope*. 2016.
235. Gluck N, Fishman S, Melhem A, Goldfarb S, Halpern Z, Santo E. A novel colonoscope with panoramic visualization detected more simulated polyps than conventional colonoscopy in a live swine model. *Endoscopy International Open*. 2015;03(06): E642–E645. <https://doi.org/10.1055/s-0034-1393080>.
236. Ciocîrlan M. Low-cost disposable endoscope: pros and cons. *Endoscopy International Open*. 2019;07(09): E1184–E1186. <https://doi.org/10.1055/a-0959-6003>.
237. Boškoski I, Costamagna G. Endoscopy robotics: Current and future applications. *Digestive Endoscopy*. 2019;31(2): 119–124. <https://doi.org/10.1111/den.13270>.
238. Cosentino F, Tumino E, Passoni GR, Morandi E, Capria A. Functional evaluation of the Endotics System, a new disposable self-propelled robotic colonoscope: In vitro tests and clinical trial. *International Journal of Artificial Organs*. 2009;32(8): 517–527. <https://doi.org/10.1177/039139880903200806>.
239. Tumino E, Sacco R, Bertini M, Bertoni M, Parisi G, Capria A. Endotics system vs colonoscopy for the detection of polyps. *World Journal of Gastroenterology*. 2010;16(43): 5452–5456. <https://doi.org/10.3748/wjg.v16.i43.5452>.
240. Tumino E, Parisi G, Bertoni M, Bertini M, Metrangolo S, Ierardi E, et al. Use of robotic colonoscopy in patients with previous incomplete colonoscopy. *European review for medical and pharmacological sciences*. 2017;21(4): 819–826.
241. Wong JYY, Ho KY. Robotics for advanced therapeutic colonoscopy. *Clinical Endoscopy*. 2018;51(6): 552–557. <https://doi.org/10.5946/ce.2018.089>.

242. Khanicheh A, Shergill AK. Endoscope design for the future. *Techniques in Gastrointestinal Endoscopy*. 2019;21: 167–173. <https://doi.org/10.1016/j.tgie.2019.05.003>.
243. USFDA. K173085 invendoscopy E210 System. 2018;
244. Gifari MW, Naghibi H, Stramigioli S, Abayazid M. A review on recent advances in soft surgical robots for endoscopic applications. *International Journal of Medical Robotics and Computer Assisted Surgery*. 2019;(April): 1–11. <https://doi.org/10.1002/rcs.2010>.
245. Peters BS, Armijo PR, Krause C, Choudhury SA, Oleynikov D. Review of emerging surgical robotic technology. *Surgical Endoscopy*. 2018;32(4): 1636–1655. <https://doi.org/10.1007/s00464-018-6079-2>.
246. Groth S, Rex DK, Rösch T, Hoepffner N. High cecal intubation rates with a new computer-assisted colonoscope: A feasibility study. *American Journal of Gastroenterology*. 2011;106(6): 1075–1080. <https://doi.org/10.1038/ajg.2011.52>.
247. Straulino F, Genthner A, Kiesslich R, Eickhoff A. Erratum: Colonoscopy with the single use endoscope Invendoscope SC210. *Gastrointestinal Endoscopy*. 2019;89(6): AB718. <https://doi.org/10.1016/j.gie.2019.04.229>.
248. Straulino F, Genthner A, Kiesslich R, Eickhoff A. Colonoscopy with the sterile single use endoscope Invendoscope Sc210. *Gastrointestinal Endoscopy*. 2018;87(6): AB257. <https://doi.org/10.1016/j.gie.2018.04.459>.
249. Straulino F, Genthner A, Ralf K, Eickhoff A. Colonoscopy With the Single Use Endoscope Invendoscope Sc210 in Routine Clinical Practice. *ESGE Days 2019*. 2019;51(04): 1681468. <https://doi.org/10.1055/s-0039-1681468>.
250. Mascagni P, Lim SG, Fiorillo C, Zanne P, Nageotte F, Zorn L, et al. Democratizing Endoscopic Submucosal Dissection: Single-Operator Fully Robotic Colorectal Endoscopic Submucosal Dissection in a Pig Model. *Gastroenterology*. 2019;156(6): 1569–1571.e2. <https://doi.org/10.1053/j.gastro.2018.12.046>.
251. Mathelin MD. *Single Port and Transluminal Robotic Assistant for Surgeons: A Modular and Flexible Telemanipulated Robotic Device for Intraluminal Surgery*. Handbook of Robotic and Image-Guided Surgery. Elsevier Inc.; <https://doi.org/10.1016/B978-0-12-814245-5.00008-6>.
252. Patel N, Darzi A, Teare J. The endoscopy evolution: ‘the superscope era’. *Frontline Gastroenterology*. 2015;6(2): 101–107. <https://doi.org/10.1136/flgastro-2014-100448>.
253. Wai P, Chiu Y. *Applications of Flexible Robots*. Handbook of Robotic and Image-Guided Surgery. Elsevier Inc.; <https://doi.org/10.1016/B978-0-12-814245-5.00018-9>.
254. Légner A, Diana M, Halvax P, Liu YY, Zorn L, Zanne P, et al. Endoluminal surgical triangulation 2.0: A new flexible surgical robot. Preliminary pre-clinical results with colonic submucosal dissection. *International Journal of Medical Robotics and Computer Assisted Surgery*. 2017;13(3): 1–8. <https://doi.org/10.1002/rcs.1819>.

255. Zorn L, Nageotte F, Zanne P, Legner A, Dallemagne B, Marescaux J, et al. A Novel Telemanipulated Robotic Assistant for Surgical Endoscopy: Preclinical Application to ESD. *IEEE Transactions on Biomedical Engineering*. 2018;65(4): 797–808. <https://doi.org/10.1109/TBME.2017.2720739>.
256. Berthet-Rayne P, Gras G, Leibrandt K, Wisanuvej P, Schmitz A, Seneci CA, et al. The i 2 Snake Robotic Platform for Endoscopic Surgery. *Annals of Biomedical Engineering*. 2018;46(10): 1663–1675. <https://doi.org/10.1007/s10439-018-2066-y>.
257. Patel N, Seneci CA, Shang J, Leibrandt K, Yang GZ, Darzi A, et al. Evaluation of a novel flexible snake robot for endoluminal surgery. *Surgical Endoscopy*. 2015; <https://doi.org/10.1007/s00464-015-4088-y>.
258. Berthet-Rayne P, Leibrandt K, Kim K, Seneci CA, Shang J, Yang GZ. Rolling-Joint Design Optimization for Tendon Driven Snake-Like Surgical Robots. *IEEE International Conference on Intelligent Robots and Systems*. 2018; 4964–4971. <https://doi.org/10.1109/IROS.2018.8593517>.
259. Berthet-Rayne P, Yang GZ. *Vision Based Shape Reconstruction of Tendon Driven Snake-Like Surgical Robots*. 2017. <https://doi.org/10.31256/hsmr2017.29>.
260. Low SC, Tang SW, Thant ZM, Phee L, Ho KY, Chung SC. Master-slave robotic system for therapeutic gastrointestinal endoscopic procedures. *Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings*. 2006; 3850–3853. <https://doi.org/10.1109/IEMBS.2006.259233>.
261. Yang K, Sun ZL, Kencana AP, Huynh VA, Rasouli M, Phee SJ, et al. Enhancement of spatial orientation and haptic perception for master-slave robotic Natural Orifice Transluminal Endoscopic Surgery (NOTES). *2010 IEEE Conference on Robotics, Automation and Mechatronics, RAM 2010*. 2010; 15–18. <https://doi.org/10.1109/RAMECH.2010.5513223>.
262. Wang Z, Phee SJ, Lomanto D, Goel R, Rebala P, Sun ZL, et al. Endoscopic submucosal dissection of gastric lesions by using a master and slave transluminal endoscopic robot: An animal survival study. *Endoscopy*. 2012;44(7): 690–694. <https://doi.org/10.1055/s-0032-1309404>.
263. Phee SJ, Ho KY, Lomanto D, Low SC, Huynh VA, Kencana AP, et al. Natural orifice transgastric endoscopic wedge hepatic resection in an experimental model using an intuitively controlled master and slave transluminal endoscopic robot (MASTER). *Surgical Endoscopy*. 2010;24(9): 2293–2298. <https://doi.org/10.1007/s00464-010-0955-8>.
264. Wang Z, Phee SJ, Lomanto D, Goel R, Rebala P, Sun ZL, et al. Endoscopic submucosal dissection of gastric lesions by using a master and slave transluminal endoscopic robot: An animal survival study. *Endoscopy*. 2012;44(7): 690–694. <https://doi.org/10.1055/s-0032-1309404>.
265. Chiu PWY, Phee SJ, Wang Z, Sun Z, Poon CC, Yamamoto T, et al. Feasibility of full-thickness gastric resection using master and slave transluminal endoscopic robot and

closure by overstitch: A preclinical study. *Surgical Endoscopy*. 2014;28(1): 319–324. <https://doi.org/10.1007/s00464-013-3149-3>.

266. Phee SJ, Reddy N, Chiu PWY, Rebala P, Rao GV, Wang Z, et al. Robot-Assisted Endoscopic Submucosal Dissection Is Effective in Treating Patients With Early-Stage Gastric Neoplasia. *Clinical Gastroenterology and Hepatology*. 2012;10(10): 1117–1121. <https://doi.org/10.1016/j.cgh.2012.05.019>.
267. Chiu P, Phee S, Bhandari P, Sumiyama K, Ohya T, Wong J, et al. Enhancing proficiency in performing endoscopic submucosal dissection (ESD) by using a prototype robotic endoscope. *Endoscopy International Open*. 2015;03(05): E439–E442. <https://doi.org/10.1055/s-0034-1393178>.
268. Chiu PWYW, Phee SJ, Ho KY. COLONIC ENDOSCOPIC SUBMUCOSAL DISSECTION USING EASE ROBOTIC SYSTEM - A PRECLINICAL STUDY. *Gastrointestinal Endoscopy*. 2019;89(6): AB658–AB659. <https://doi.org/10.1016/j.gie.2019.03.1160>.
269. Carmichael H, D'Andrea AP, Skancke M, Obias V, Sylla P. Feasibility of transanal total mesorectal excision (taTME) using the Medrobotics Flex® System. *Surgical Endoscopy*. 2019;(0123456789). <https://doi.org/10.1007/s00464-019-07019-y>.
270. Cengiz TB, Steele SR, Gorgun E. Implementation of Novel Robotic Systems in Colorectal Surgery. In: *Handbook of Robotic and Image-Guided Surgery*. Elsevier Inc.; 2020. p. 147–158. <https://doi.org/10.1016/b978-0-12-814245-5.00009-8>.
271. Lang S, Mattheis S, Hasskamp P, Lawson G, Güldner C, Mandapathil M, et al. A european multicenter study evaluating the flex robotic system in transoral robotic surgery. *Laryngoscope*. 2017;127(2): 391–395. <https://doi.org/10.1002/lary.26358>.
272. Paull JO, Graham A, Parascandola SA, Hota S, Pudalov N, Arnott S, et al. The outcomes of two robotic platforms performing transanal minimally invasive surgery for rectal neoplasia : a case series of 21 patients. *Journal of Robotic Surgery*. 2019;(0123456789): 1–6. <https://doi.org/10.1007/s11701-019-01021-1>.
273. Turiani Hourneaux de Moura D, Aihara H, Jirapinyo P, Farias G, Hathorn KE, Bazarbashi A, et al. Robot-assisted endoscopic submucosal dissection versus conventional ESD for colorectal lesions: outcomes of a randomized pilot study in endoscopists without prior ESD experience (with video). *Gastrointestinal Endoscopy*. 2019;90(2): 290–298. <https://doi.org/10.1016/j.gie.2019.03.016>.
274. Mylonas GP, Patel N, Teare J, Darzi A. CYCLOPS: AN ENDOSCOPE ATTACHMENT FOR ENDOSCOPIC SUBMUCOSAL DISSECTION. In: *SAGES 2017 Annual Meeting in Houston*. Houston; 2017.
275. Patel NK. *Advances in Endoluminal Surgery*. Imperial College London; 2018.
276. Vrieling T, Zhao M, Darzi A, Mylonas GP. ESD CYCLOPS: A New Robotic Surgical System for GI Surgery. *IEEE International Conference on Robotics and Automation*. 2018; 150–157. <https://doi.org/10.1109/ICRA.2018.8462698>.

277. Yang GZ, Cambias J, Cleary K, Daimler E, Drake J, Dupont PE, et al. Medical robotics-Regulatory, ethical, and legal considerations for increasing levels of autonomy. *Science Robotics*. 2017;2(4): 1–2. <https://doi.org/10.1126/scirobotics.aam8638>.
278. Ma X, Wang P, Ye M, Chiu PWY, Li Z. Shared autonomy of a flexible manipulator in constrained endoluminal surgical tasks. *IEEE Robotics and Automation Letters*. 2019;4(3): 3106–3112. <https://doi.org/10.1109/LRA.2019.2924851>.
279. Ciuti G, Skonieczna-Żydecka K, Marlicz W, Iacovacci V, Liu H, Stoyanov D, et al. Frontiers of Robotic Colonoscopy: A Comprehensive Review of Robotic Colonoscopes and Technologies. *Journal of Clinical Medicine*. 2020;9(6): 1648. <https://doi.org/10.3390/jcm9061648>.
280. Heung H, Chiu PWY, Li Z. Design and prototyping of a soft earthworm-like robot targeted for GI tract inspection. *2016 IEEE International Conference on Robotics and Biomimetics, ROBIO 2016*. 2016; 497–502. <https://doi.org/10.1109/ROBIO.2016.7866371>.
281. Miriyev A, Stack K, Lipson H. Soft material for soft actuators. *Nat Commun*. 2017;8(1): 596.
282. Bernth JE, Arezzo A, Liu H. A novel robotic meshworm with segment-bending anchoring for colonoscopy. *IEEE Robotics and Automation Letters*. 2017;2(3): 17–18. <https://doi.org/10.1109/LRA.2017.2678540>.
283. Putzu F, Konstantinova J, Althoefer K. Soft Particles for Granular Jamming. In: Althoefer K, Konstantinova J, Zhang K (eds.) *Towards Autonomous Robotic Systems*. Cham: Springer International Publishing; 2019. p. 65–74.
284. Arezzo A, Mintz Y, Allaix ME, Arolfo S, Bonino M, Gerboni G, et al. Total mesorectal excision using a soft and flexible robotic arm: a feasibility study in cadaver models. *Surgical Endoscopy*. 2017;31(1): 264–273. <https://doi.org/10.1007/s00464-016-4967-x>.
285. Sivananthan, Arun, Kogkas A, Glover B, Darzi A, Mylonas G, Patel N. Gaze Controlled Endoscopy. *Surgical Life*. 2021;(59): 28–31.
286. Sivananthan A, Kogkas A, Glover B, Darzi A, Mylonas G, Patel N. A novel gaze-controlled flexible robotized endoscope; preliminary trial and report. *Surgical Endoscopy*. 2021;(0123456789). <https://doi.org/10.1007/s00464-021-08556-1>.
287. Teoh AYB, Chan SM, Yip HC, Wong VWY, Chiu PWY, Ng EKW. Randomized controlled trial of EndoWrist-enabled robotic versus human laparoendoscopic single-site access surgery (LESS) in the porcine model. *Surgical Endoscopy*. 2018;32(3): 1273–1279. <https://doi.org/10.1007/s00464-017-5803-7>.
288. Fuchs K hermann, Neki K, Lee A, Profeta RD. NEW ENDOSUTURE INSTRUMENT SYSTEM FOR FLEXIBLE ENDOSCOPIC SUTURING IN THE GI-TRACT. In: 2017.

289. Sivananthan A, Nazarian S, Ayaru L, Patel K, Ashrafian H, Darzi A, et al. Does computer-aided diagnostic endoscopy improve the detection of commonly missed polyps? A meta-analysis. *Clinical Endoscopy*. 2022;55(3): 355–364. <https://doi.org/10.5946/ce.2021.228>.
290. Oude Vrielink T, Puyal J, Kogkas A, Darzi A, Mylonas G. *Intuitive Gaze-Control of a Robotized Flexible Endoscope*. 2018. <https://doi.org/10.1109/IROS.2018.8594426>.
291. *ROBOTIS e-Manual*. ROBOTIS e-Manual. <https://manual.robotis.com/docs/en/dxl/rx/rx-24f/> [Accessed 11th June 2023].
292. Kogkas A, Darzi A, Mylonas GP. Gaze-contingent perceptually enabled interactions in the operating theatre. *International Journal of Computer Assisted Radiology and Surgery*. 2017;12(7): 1131–1140. <https://doi.org/10.1007/s11548-017-1580-y>.
293. Kogkas A, Ezzat A, Thakkar R, Darzi A, Mylonas G. Free-View, 3D Gaze-Guided Robotic Scrub Nurse. In: *Medical Image Computing and Computer Assisted Intervention*. 2019. p. 164–172.
294. Ezzat A, Thakkar R, Kogkas A, Mylonas G. *Perceptions of surgeons and scrub nurses towards a novel eye-tracking based robotic scrub nurse platform*. WILEY; 2019. http://gateway.webofknowledge.com/gateway/Gateway.cgi?GWVersion=2&SrcApp=PARTNER_APP&SrcAuth=LinksAMR&KeyUT=WOS:000484980700300&DestLinkType=FullRecord&DestApp=ALL_WOS&UsrCustomerID=1ba7043ffcc86c417c072aa74d649202
295. Reilink R, de Bruin G, Franken M, Mariani MA, Misra S, Stramigioli S. Endoscopic camera control by head movements for thoracic surgery. In: *2010 3rd IEEE RAS EMBS International Conference on Biomedical Robotics and Biomechatronics*. 2010. p. 510–515. <https://doi.org/10.1109/BIOROB.2010.5627043>.
296. Hart SG, Staveland LE. Development of NASA-TLX (Task Load Index): Results of Empirical and Theoretical Research. *Advances in Psychology*. 1988;52: 139–183. [https://doi.org/10.1016/S0166-4115\(08\)62386-9](https://doi.org/10.1016/S0166-4115(08)62386-9).
297. Zheng B, Rieder E, Cassera MA, Martinec DV, Lee G, Panton ONM, et al. Quantifying mental workloads of surgeons performing natural orifice transluminal endoscopic surgery (NOTES) procedures. *Surgical Endoscopy*. 2012;26(5): 1352–1358. <https://doi.org/10.1007/s00464-011-2038-x>.
298. Jirapinyo P, Kumar N, Thompson CC. Validation of an endoscopic part-task training box as a skill assessment tool. *Gastrointestinal endoscopy*. 2015;81(4): 967–973. <https://doi.org/10.1016/j.gie.2014.08.007>.
299. Mohamed R, Raman M, Anderson J, McLaughlin K, Rostom A, Coderre S. Validation of the National Aeronautics and Space Administration Task Load Index as a tool to evaluate the learning curve for endoscopy training. *Canadian journal of gastroenterology & hepatology*. 2014;28(3): 155–159. <https://doi.org/10.1155/2014/892476>.
300. Jirapinyo P, Abidi WM, Aihara H, Zaki T, Tsay C, Imaeda AB, et al. Preclinical endoscopic training using a part-task simulator: learning curve assessment and determination of

threshold score for advancement to clinical endoscopy. *Surgical Endoscopy*. 2017;31(10): 4010–4015. <https://doi.org/10.1007/s00464-017-5436-x>.

301. Van Der Laan JD, Heino A, De Waard D. A simple procedure for the assessment of acceptance of advanced transport telematics. *Transportation Research Part C: Emerging Technologies*. 1997;5(1): 1–10. [https://doi.org/10.1016/S0968-090X\(96\)00025-3](https://doi.org/10.1016/S0968-090X(96)00025-3).
302. Stoyanov D, Mylonas GP, Yang GZ. Gaze-contingent 3D control for focused energy ablation in robotic assisted surgery. *Medical image computing and computer-assisted intervention : MICCAI ... International Conference on Medical Image Computing and Computer-Assisted Intervention*. 2008;11(Pt 2): 347–355. https://doi.org/10.1007/978-3-540-85990-1_42.
303. Visentini-Scarzanella M, Mylonas GP, Stoyanov D, Yang GZ. i-BRUSH: a gaze-contingent virtual paintbrush for dense 3D reconstruction in robotic assisted surgery. *Medical image computing and computer-assisted intervention : MICCAI ... International Conference on Medical Image Computing and Computer-Assisted Intervention*. 2009;12(Pt 1): 353–360. https://doi.org/10.1007/978-3-642-04268-3_44.
304. Mylonas GP, Kwok KW, James DRC, Leff D, Orihuela-Espina F, Darzi A, et al. Gaze-Contingent Motor Channelling, haptic constraints and associated cognitive demand for robotic MIS. *Medical image analysis*. 2012;16(3): 612–631. <https://doi.org/10.1016/j.media.2010.07.007>.
305. Sivananthan A, Rubio-Solis A, Darzi A, Mylonas G, Patel N. Eye-controlled endoscopy - a benchtop trial of a novel robotic steering platform - iGAZE2. *Journal of Robotic Surgery*. 2024;18(1): 266. <https://doi.org/10.1007/s11701-024-02022-5>.
306. Sidhu R, Turnbull D, Haboubi H, Leeds JS, Healey C, Hebbar S, et al. British Society of Gastroenterology guidelines on sedation in gastrointestinal endoscopy. *Gut*. 2024;73(2): 1–27. <https://doi.org/10.1136/gutjnl-2023-330396>.

12. Appendices

Appendix 1

Question 1		MeSH terms
Population	GI endoscopy (simulated or human)	
Intervention	gaze analysis/ eye tracking	Gaze, Gaze Analysis, Eye Tracking, Gaze Tracking, Visual Patterns, Gaze Control
Comparator group	standard endoscopy	
Outcome	scoping/ systematic review of all available evidence	

Sources of Literature:

The following clinical databases will be searched:

1. **Medline:** <https://www.ncbi.nlm.nih.gov/pubmed/>
2. **Cochrane Reviews** <https://www.cochranelibrary.com>
3. **Embase**

Databases will be searched using Medical Search Headings (MeSH) where possible:

Medline:

1 exp Endoscopy, Gastrointestinal/ 98063

2 exp Endoscopy, Digestive System/ 121572

3 exp Colonoscopy/ 33796

4 exp Sigmoidoscopy/ 4879

5 exp Duodenoscopy/ 3145

6 exp Esophagoscopy/ 15352

7 exp Gastroscopy/ 17720

8 exp Proctoscopy/ 3055

9 exp Capsule Endoscopy/ 3442

10 ((GI or gastrointestinal) adj3 endoscop*).mp. 30970

11 (intestin* adj3 endoscop*).mp. 1060

12 colonoscop*.mp. 46670

13 duodenoscop*.mp. 4614

14 eosophagogastroduodenoscop*.mp. 1

15 esophagoduodenoscop*.mp. 45

16 esophagogastroduodenoscop*.mp. 4774

17 esophagoscop*.mp. 16554

18 gastroscop*.mp. 22661

19 oesophagoduodenoscop*.mp. 12

20 oesophagogastroduodenoscop*.mp. 463

21 oesophagoscop*.mp. 531

22 rectoscop*.mp.584

23 sigmoidoscop*.mp. 7485

24 (upper adj3 endoscop*).mp. 12717

25 exp Gastrointestinal Tract/ or exp Gastrointestinal Diseases/ or exp Digestive System/
2062767

26 exp Endoscopy/392522

27 25 and 26 145466

28 gaze analys*.mp. 47

29 (eye adj2 track*).mp. 8614

30 eyetrack*.mp. 410

31 eye movement measurement*.mp. 1994

32 eye movement track*.mp. 71

33 optical track*.mp. 991

34 gaze track*.mp.284

35 Gaze control.mp. 363

36 visual track*.mp. 932

37 visual pattern*.mp. 1401

38 exp Eye Movement Measurements/ 13450

39 exp Eye Movements/ 50386

40 eye gaze.mp. 1552

41 eye movement*.mp. 55445

42 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 83353

43 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 27 204097

44 42 and 43 39

Cochrane review:

#1 MeSH descriptor: [Endoscopy, Gastrointestinal] explode all trees 4926

#2 MeSH descriptor: [Endoscopy, Digestive System] explode all trees 5800

#3 MeSH descriptor: [Colonoscopy] explode all trees 2269

#4 MeSH descriptor: [Sigmoidoscopy] explode all trees 298

#5 MeSH descriptor: [Duodenoscopy] explode all trees 184

#6 MeSH descriptor: [Duodenoscopy] explode all trees 184

#7 MeSH descriptor: [Gastrosocopy] explode all trees 872

#8 MeSH descriptor: [Proctoscopy] explode all trees 68

#9 MeSH descriptor: [Capsule Endoscopy] explode all trees 139

#10 (GI or gastrointestinal) near/2 endoscop* 5400

#11 intestin* near/2 endoscop* 239

#12 colonoscop* or duodenoscop* or eosophagoduodenoscop* or
eosophagogastroduodenoscop* or eosphagoscop* or esophagoduodenoscop* or
esophagogastroduodenoscop* or esophagoscop* or gastroscop* or oesophagoduodenoscop*
or oesophagogastroduodenoscop* or oesophagoscop* or proctoscop* or rectoscop* or
sigmoidoscop* 12132

#13 upper near/2 endoscop* 1666

#14 MeSH descriptor: [Gastrointestinal Diseases] explode all trees 37665

#15 MeSH descriptor: [Gastrointestinal Tract] explode all trees 12480

#16 #14 or #15 45348

#17 MeSH descriptor: [Endoscopy] explode all trees 19324

#18 #17 and #16 5515

#19 #18 or #13 or #12 or #10 or #9 or #8 or #7 or #6 or #5 or #4 or #3 or #2 or #1 18846

#20 "gaze analysis" or "gaze analyses" 3

#21 eye near/2 track* 866

#22 eyetrack* 381

#23 "eye movement measurement" or "eye movement measurements" 63

#24 "eye movement track" or "eye movement tracking" 4

#25 "optical track" or "optical tracking" 32

#26 "gaze track" or "gaze tracking" 12

#27 "gaze control" 21

#28 "visual track" or "visual tracking" 67

#29 "visual pattern" or "visual patterns" 70

#30 MeSH descriptor: [Eye Movement Measurements] explode all trees 354

#31 MeSH descriptor: [Eye Movements] explode all trees 1344

#32 "eye gaze" 131

#33 eye movement* 4636

#34 #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 5849

#35 #19 and #34 13

Embase:

1 exp gastrointestinal endoscopy/172270

2 exp digestive tract endoscopy/ 245359

3 exp colonoscopy/ 95020

4 exp sigmoidoscopy/ 13208

5 exp duodenoscopy/ 4441

6 exp esophagoscopy/ 12939

7 exp gastroscopy/ 24574

8 exp capsule endoscopy/10395

9 exp esophagogastrroduodenoscopy/ 18022

10 (gastrointestinal adj3 endoscop*).mp. 48406

11 (GI adj3 endoscop*).mp. 6003

12 colonoscop*.mp. 105324

13 duodenoscop*.mp. 7471

14 eosophagogastrroduodenoscop*.mp. 3

15 eosphagoscop*.mp. 1

16 esophagoduodenoscop*.mp. 198

17 esophagogastrroduodenoscop*.mp. 19776

18 esophagoscop*.mp. 14161

19 gastroscop*.mp. 31014

20 oesophagoduodenoscop*.mp. 23

21 oesophagogastroduodenoscop*.mp. 745

22 oesophagoscop*.mp. 611

23 proctoscop*.mp. 1239

24 rectoscop*.mp.3110

25 sigmoidoscop*.mp. 14934

26 (upper adj3 endoscop*).mp. 25551

27 exp gastrointestinal tract/ 70272

28 exp gastrointestinal disease/ 95656

29 exp endoscopy/720874

30 27 or 28 163299

31 29 and 30 22579

32 exp intestine endoscopy/ 119959

33 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 31 or 32 286014

34 gaze analys*.mp. 58

35 (eye adj2 track*).mp. 16668

36 exp eye tracking/ 11553

37 eyetrack*.mp. 675

38 eye movement measurement*.mp. 114

39 eye movement track*.mp. 98

40 optical track*.mp. 1377

41 gaze track*.mp.352

42 gaze control.mp. 445

43 visual track*.mp. 1164

44 visual pattern*.mp. 1633

45 exp oculography/ 18207

46 exp eye movement/ 58826

47 eye gaze.mp. 1820

48 eye movement*.mp. 76411

49 exp eye-tracking technology/ or exp eye tracking system/ 989

50 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
102889

51 3 and 50 119

Appendix 2

EMBASE & Medline

- #1 Colonic Polyps/
- #2 colorect* or colon or colonoscop* or large bowel or rectal or rectum or anal or anus or large intestine and polyp
- #3 1 or 2
- #4 exp algorithms/
- #5 artificial intelligence or machine learning or neural network*
- #6 4 or 5
- #7 computer aided or computer assisted and diagnos* or detect*
- #8 diagnosis, computer-assisted/ or image interpretation, computer-assisted/ or neuronavigation/
- #9 image processing, computer-assisted/ or data compression/ or image enhancement/ or imaging, three-dimensional/
- #10 7 or 8 or 9
- #11 3 and 6 and 10

The Cochrane Library

- #1 Colonic Polyps
- #2 colorect* or colon or colonoscop* or large bowel and polyp
- #3 1 or 2
- #4 exp artificial intelligence
- #5 artificial intelligence or machine learning or neural network*
- #6 4 or 5
- #7 exp diagnosis, computer-assisted
- #8 computer aided or computer assisted and diagnos* or detect*
- #9 7 or 8
- #10 3 or 6 or 9

Appendix 3

Quality Assessment

Study	Randomisation (2)	Blinding (2)	An account of all patients (1)	Total / 5
Wang et al. 2019	2	1	1	4
Wang et al. 2020	2	2	1	5
Su et al. 2020	2	2	1	5
Gong et al. 2020	2	2	1	5
Liu et al. 2020	1	0	1	2
Luo et al. 2020	2	0	1	3
Repici et al. 2020	2	1	1	4

Assessment of bias for RCTs using the Jadad scale; score ≥ 3 = good quality.

Appendix 3



Dr Nisha Patel
St Mary's Hospital
Praed Street
London
W21NYN/A

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

04 March 2022

Dear Dr Patel,

**HRA and Health and Care
Research Wales (HCRW)
Approval Letter**

Study title:	Eye gaze technology for endoscopic inspection of the gastrointestinal tract
IRAS project ID:	288108
Protocol number:	20SM6304
REC reference:	22/NW/0002
Sponsor	Imperial College London

I am pleased to confirm that [HRA and Health and Care Research Wales \(HCRW\) Approval](#) has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.