IMPROVING THE QUALITY OF COLONOSCOPY

Alexandre Nuno Fonseca e Silva de Oliveira Ferreira

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LIST OF PUBLICATIONS

1. Ferreira AO, Reves J, Nascimento C, Frias-Gomes C, Costa-Santos MP, Ramos L, Palmela C, Gloria L, Cravo M, Dinis-Ribeiro M, Canena J. Narrow Band Imaging versus White Light for the Detection of Sessile Serrated Colorectal Lesions: a Randomized Clinical Trial. GE Portuguese Journal of Gastroenterology

- Prémio Nacional de Gastrenterologia 2021 awarded by Sociedade Portuguesa de Gastrenterologia
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2. Ferreira AO, Costa-Santos MP, Palmela C, Gloria L, Cravo M, Canena J, Dinis-Ribeiro M, Canena J. Endocuff-Assisted Colonoscopy Does Not increase the Sessile Serrated Lesion Detection Rate – A Randomized Controlled Trial. Submitted to Scientific Reports.

Oral presentation at Semana Digestiva 2019, Vilamoura, Portugal

- Poster presentation at United European Gastroenterology Week 2019. Barcelona, Spain

3. Ferreira AO, Costa-Santos MP, Gomes C, Morão B, Glória L, Cravo M, et al. Participation in clinical trials increases the detection of pre-malignant lesions during colonoscopy. Revista espanola de enfermedades digestivas : organo oficial de la Sociedad Espanola de Patologia Digestiva. 2021.

- Poster presentation at ENDO 2020, Rio de Janeiro, Brazil

4. Oliveira Ferreira A, Fidalgo C, Palmela C, Costa Santos MP, Torres J, Nunes J, et al. Adenoma Detection Rate: I Will Show You Mine if You Show Me Yours. GE - Portuguese Journal of Gastroenterology. 2017;24:61-7.

5. Ferreira AO, Torres J, Barjas E, Nunes J, Gloria L, Ferreira R, et al. Non-anesthesiologist administration of propofol sedation for colonoscopy is safe in low risk patients: results of a noninferiority randomized controlled trial. Endoscopy. 2016;48:747-53.

- Oral presentation at Semana Digestiva 2015, Porto, Portugal
- Oral presentation at Semana Digestiva 2016, Albufeira, Portugal
- Poster presentation at United European Gastroenterology Week 2015. Barcelona, Spain

6. Ferreira AO, Torres J, Dinis-Ribeiro M, Cravo M. Endoscopic sedation and monitoring practices in Portugal: a nationwide web-based survey. European journal of gastroenterology & hepatology. 2015;27:265-70.

- Oral presentation at XXIX Reunião Anual do NGHD 2014. Torres Vedras, Portugal
- Oral presentation at Semana Digestiva 2016, Albufeira, Portugal

PROLOGUE AND ACKNOWLEDGEMENTS

Since the early stages of my education, I have strived for a critical and analytical mind. However, as I started the Gastroenterology residency, I also loved the daily activities as a practicing clinician in a speciality with an increasingly greater array of interventional possibilities and an ever-evolving endoscopic armamentarium. Fortunately for me, my residency was based in Portimão which gave me the opportunity to perform 2.5 years of my training in other centres in Portugal at Centro Hospitalar Lisboa Norte, Hospital Beatriz Ângelo and Instituto Português de Oncologia de Lisboa and abroad at *Hôpital Erasme* in Brussels and at *Klinikum Hannover* in Germany.

During the one-year period I spent in Centro Hospitalar Lisboa Norte, I started to develop critical analytical skills as my interest in research developed. I performed a few observational studies and undertook several courses on Clinical Research. Gradually, Clinical Research began to be increasingly important to me as a means to help me question and try to improve my clinical practice. I was lucky to have mentors early on like Professor Rui Tato Marinho and Professor Marília Cravo who were very supportive and continuously defiant. Furthermore, Professor Marília's enthusiasm and support for my first major project was a major catalyst and without her many of the projects I undertook would not have been possible. Thanks to them and my residency mentor – Dr Helena Tavares, I developed my research skills and in 2014 joined the Harvard Medical School – Clinical Scholars Research Training which had a major impact in my training.

At the time I was discovering my passion for Gastrointestinal Endoscopy and eager to apply my research knowledge in a meaningful and useful way.

In 2015 I finished my residency and joined a "research friendly" department at Hospital Beatriz Ângelo and as a natural continuum of my career as a clinician-researcher I started the Doctoral Programme at Nova Medical School.

As a PhD candidate I was also fortunate to have as mentors two of the most influential endoscopists and researchers in Portugal and in Europe and whom I am lucky to call my friends: Professor Jorge Canena and Professor Mário Dinis Ribeiro.

My training continued over the following years with support from the Head of the Department and from the Clinical Director Professor Rui Maio who was also very supportive of my research and endoscopic training. They made it possible for me to

benefit from two Fellowship grants from the ESGE - Endoscopic Society of Gastrointestinal Endoscopy – the first one in 2015 at Leeds Teaching Hospitals and later in 2017 at *Cliniques Universitaires St. Luc* in Brussels. The experience I have had in 4 hospitals in Portugal and 4 abroad was very important, not only because it allowed me to learn new technical skills, to develop my network and discuss ideas with top professionals in the field, but also to question and evaluate the variability in clinical practice between hospitals and countries. These differences were also motivations for some of my research work like the studies on sedation and a study on NBI for squamous cell neoplasia in the esophagus.

Most of the work I performed over these years was devoted to endoscopy and a significant part of it was specifically undertaken to evaluate the safety and the impact on colonoscopy quality of different techniques and interventions.

This thesis is divided in four chapters. The first is an introduction to colonoscopy as a screening tool for colorectal cancer. The second and third chapters are the combination of our research work and the published papers. Finally, I draw a unifying conclusion on how these studies contribute to our knowledge and clinical practice and dwell into considerations on future research ideas and projects.

Firstly, we evaluated the safety of sedation for colonoscopy. These studies were motivated following my fellowship in Germany with Professor Riphaus, who is the lead author of the ESGE European guidelines on sedation in endoscopy. We performed a national survey on sedation practices in Portugal and a randomized trial on propofol sedation for colonoscopy.

Later, as we work with different endoscopic equipment across several institutions, we noticed that the detection of pre-malignant lesions was affected by the quality of the equipment and the quality of the imaging. Furthermore, it seemed that this variability was even greater for a specific group of lesions called sessile serrated lesions. This variability has been previously shown and has several reasons to support it. To further study this issue, we decided to perform an observational study to determine our quality metrics, including the detection rates of polyps, adenomas and sessile serrated lesions. Afterwards, we performed two prospective interventional studies to determine the effect on the detection of sessile serrated lesions of two specific interventions: chromoendoscopy with last generation narrow band imaging (NBI) and a colonoscope distal attachment called Endocuff Vision.

After these studies we hypothesized whether the participation on such prospective trials could improve the overall quality of colonoscopy and we did one last study to evaluate this hypothesis.

Finally, I would like to acknowledge some of the most determinant people for this work. The ones that motivated me in the early stages of my career: Dr Helena Tavares and Professor Rui Tato Marinho; a critical person and mentor that was Professor Marília Cravo with her outstanding energy and positivity. She is an inspiring leader who sets the standard high and motivates all who work with her. She was always supportive when needed and she has helped me understand my own priorities and my goals. Dr Luisa Glória who is currently the head of the department at Hospital Beatriz Ângelo; Dr Helena Oliveira who helped countless times and reviewed hundreds of pathology specimens; my colleagues, residents and all the nurses and staff, especially Elidio Barjas, Lídia Roque Ramos, Carolina Palmela, Maria Pia Santos and Catarina Gomes; the Clinical Director Professor Rui Maio who understood our needs and aims and was always supportive and a true facilitator.

Professor Jorge Canena who was a supportive friend since day one of this endeavour as was Professor Mário Dinis Ribeiro to whom I look up to.

Last but not least, I would also like to thank my family, especially my parents and my close friends who supported and encouraged me even before I decided to embark on this endeavour.

ABBREVIATIONS

AADR – advanced adenoma detection rate

ACS – American Cancer Society

ACG – American College of Gastroenterology

ACLS – advanced cardiac life support

ADR – adenoma detection rate

AE – adverse events

ASA – American Society of Anaesthesiology

ASGE – American Society of Gastrointestinal Endoscopy

BBPS – Boston Bowel Preparation Score

BMI – body mass index

CC – capsule colonoscopy

CIMP – CpG island methylator phenotype

CIN – chromosome instability

CIR – Cecal intubation rate

CRC – colorectal cancer

CRC DR – colorectal cancer detection rate

CTC – computed tomography colonography

HD-WL - high-definition white light

EGD – esophagogastroduodenoscopy

ESGE – European Society of Gastrointestinal Endoscopy

EV – Endocuff Vision

FDA – Food and Drug Administration

FIT – fecal immunochemical test

FOBT – fecal occult blood test

GI – gastrointestinal

LDR – lesion detection rate

MAPC – mean adenoma per colonoscopy

MD – mean difference

MLPC – mean lesion per colonoscopy

MSI-H – microsatellite instability - high

MSS – microsatellite stable

MVHP – microvesicular hyperplastic polyp

NAAP – non-anaesthesiologist administration of propofol

NBI – narrow band imaging

NSAID – non-steroidal anti-inflammatory drug

OR – odds ratio

RCT – randomized controlled trial

RR – risk ratio

SSA/P – sessile serrated adenoma/polyp

SSL – sessile serrated lesions

TSA – traditional serrated adenoma

UK – United Kingdom

USA – United States of America

USMSTF – United States Multi-Society Task Force

WHO – World Health Organization

ABSTRACT

Colorectal cancer (CRC) is a leading cause of morbidity and mortality in the world, mostly in western countries. Worldwide, CRC accounts for over 930 000 deaths/year. Colonoscopy has been shown to decrease both CRC incidence and mortality by detecting and allowing the removal of adenomas. Adenomas are part of the carcinogenesis pathway of colorectal adenocarcinoma and they are particularly amenable to screening because of their slow growth and ease of endoscopic resection. However, optical colonoscopy has been shown to miss some pre-malignant lesions in tandem studies, especially sessile serrated lesions (SSL). These lesions are different from adenomas, they are more frequent on the right colon, usually present with a flat morphology and are indistinct from the adjacent normal mucosa which makes them much harder to detect through optical colonoscopy. SSL also present a different, faster carcinogenesis pathway and as result of these characteristics, they are strongly associated with interval CRC, which is the occurrence of colorectal cancer after a screening colonoscopy and before the next scheduled screening/surveillance procedure.

New technologies and strategies have emerged to increase the sensitivity of colonoscopy for pre-cancerous lesions, especially adenomas, since their detection rate is associated with the future risk of CRC. Nevertheless, in order to increase the preventive effect of colonoscopy it is also important to detect SSL more effectively.

Herein, we present our contribution to the ongoing search for quality improvements in screening colonoscopy. We performed one national survey, three randomized trials and two observational studies to evaluate different aspects of colonoscopy safety and effectiveness.

The role of sedation in gastrointestinal endoscopy

First, we looked into the role of sedation as it is a fundamental aspect of colonoscopy safety and quality. We performed a national survey to evaluate the current sedation and monitoring practices in Portuguese endoscopy units (both in public and private practice). In this study we learned that sedation is a routine practice in colonoscopy. Propofol and midazolam are the most used drugs and the former is the agent of choice for most endoscopists but its' use is almost exclusively performed by anesthesiologists.

After this survey was performed and driven by different national practices in Europe we undertook a randomized study to compare non-anesthesiologist administered propofol sedation (NAAP) and anesthesiologist directed sedation safety and quality, in low-risk patients undergoing routine colonoscopy in Portugal. We performed a single center non-inferiority randomized controlled trial with 277 colonoscopies (150 in the NAAP group and 127 in the anesthesiologist sedation group) and there was no difference between the primary endpoints in the two groups. The incidence of AE was 39.3% in the NAAP group and 39% in the anesthesiologist sedation group (absolute difference -0.3%, 95% CI -12.0 to 11.4%; p=0.959). There was no significant difference in the main quality indicators. The adenoma detection rate (ADR) was 28.4% in group A and 23.2% in group B (p=0.331). We concluded that NAAP was non-inferior to anesthesiologist sedation in a low risk (ASA I-II) population submitted to colonoscopy. Adverse events are common but can be safely managed by a trained team and propofol provides a high-quality sedation by achieving high patient satisfaction scores and willingness to repeat the colonoscopy.

Quality indicators in colonoscopy

Following this study, we performed an observational cross-sectional study to evaluate the colonoscopy quality at our unit by measuring the currently accepted quality indicators and publish them as benchmarking indicators. In this study, the overall ADR was 36% (95% CI 32-39), the mean number of adenomas per colonoscopy was 0.66 (95% CI 0.56-0.77), the sessile serrated lesion detection rate was 1% (95% CI 0-2) and the adjusted cecal intubation rate (CIR) was 93.7% (95% CI 91.7-95.8). Most colonoscopies were performed under deep sedation (53%), and 35% were unsedated. The use of sedation (propofol or midazolam based) was associated with a higher CIR (OR 3.60, 95% CI 2.02-6.40, p < 0.001). The high frequency of poor bowel preparation and the low sessile serrated lesion detection rate were acknowledged, and actions were implemented to improve both indicators.

Improving quality in colonoscopy

The last studies were designed to evaluate whether the use of narrow band imaging and Endocuff could improve the detection of lesions, specifically sessile serrated lesions.

In the Endocuff trial we randomized 257 patients who underwent elective colonoscopy. The patients were randomly allocated to one of two groups according to the use of Endocuff Vision (EV) - standard colonoscopy vs. colonoscopy with EV. We compared the rates of detection of serrated lesions and adenomas. The number of serrated lesions per colonoscopy was not significantly higher in the EV group (0.233 vs 0.156, mean difference 0.076, p=0.381). None of the secondary endpoints regarding the detection rate of adenomas (65.9% vs 66.4%; OR 0.977, 95% CI 0.583-1.638; p=0.931) or sessile serrated lesions (12.4% vs 7.8%; OR 1.671; 95% CI 0.728-3.836; p=0.226) were superior in the EV group. We concluded that EV did not increase the detection rate of SSL.

In the NBI trial we performed a randomized clinical trial to compare the mean detection of serrated lesions and hyperplastic polyps ≥10 mm with NBI or high-definition white light (HD-WL) withdrawal. We also compared all sessile serrated lesions (SSL), adenoma and polyp prevalence and rates. Overall, 782 patients were randomized and the average number of serrated lesions and hyperplastic polyps ≥10 mm detected per colonoscopy (primary endpoint) was similar between the HD-WL and NBI group (0.118 vs 0.156, p=0.44). The adenoma detection rate (55.2% vs 53.2%, p=0.58) and SSL detection rate (6.8% vs 7.5%, p=0.502) were not different between the two study groups. Withdrawal time was higher in the NBI group (10.88 vs 9.47 min, p=0.004), with a statistically non-significant higher total procedure time (20.97 vs 19.30 min, p=0.052). The results demonstrate that routine utilization of narrow band imaging does not improve the detection of serrated class lesions or any pre-malignant lesion and increases the withdrawal time.

After these trials we decided to explore whether participating in research projects could have an impact in the quality indicators of routine colonoscopies. We performed a cross-sectional study comparing the detection of pre-malignant lesions in 147 randomly sampled non-research colonoscopies and 294 from the control groups of two prospective trials. The pre-malignant lesion detection rate was higher in the trial group with 65.6% vs 44.2% (OR 2.411; 95% CI 1.608-3.614; p<0.001), the polyp detection rate was 73.8% vs 59.9% (OR 1.889; 95% CI 1.242-2.876; p=0.003), the adenoma detection rate was 62.6% vs 44.2% (OR 2.110; 95% CI 1.411-3.155; p<0.001) and the sessile serrated lesion detection rate was 17% vs 4.1% (OR 4.816; 95% CI 2.014-11.515; p<0.001). The mean number of pre-malignant and sessile serrated lesions was 1.70 vs 1.06 (p=0.002) and 0.32 vs 0.06 (p=0.001) lesions per colonoscopy. In a multivariate analysis with each single potential confounder, there was no significant change in any of the study

outcomes. Therefore, we concluded that patients involved in colonoscopy trials may benefit from higher quality examinations, as shown by the higher detection rates. Institutions should consider supporting clinical research in colonoscopy as a simple means to improve colonoscopy quality and colorectal cancer prevention.

RESUMO

O cancro colorretal (CCR) é uma das principais causas de morbimortalidade no mundo, principalmente no Ocidente. Globalmente, o CCR é responsável por mais de 930.000 mortes por ano. A colonoscopia demonstrou diminuir a incidência e a mortalidade por CCR através da deteção e remoção de adenomas. Os adenomas inserem-se na via de carcinogénese do adenocarcinoma colorretal e o seu crescimento lento e a possibilidade de resseção endoscópica tornam a sua deteção fundamental no rastreio de CCR.

Contudo, alguns estudos demonstram que determinadas lesões pré-malignas podem não ser detetadas facilmente por colonoscopia, nomeadamente as lesões serreadas sésseis (LSS). Estas diferem dos adenomas, apresentando geralmente uma morfologia plana e são mais frequentes no cólon direito, aspetos que tornam mais difícil a sua deteção por colonoscopia ótica. Além disso, as LSS apresentam uma via de carcinogénese mais acelerada, estando, por isso, associadas a CCR de intervalo (definido como a ocorrência de CCR após uma colonoscopia de rastreio e que de desenvolve antes da colonoscopia de vigilância programada). Novas tecnologias têm sido desenvolvidas no sentido de aumentar a sensibilidade da colonoscopia para lesões pré-malignas, nomeadamente adenomas, pois o aumento da sua taxa de deteção traduz-se na diminuição do risco de CCR. Porém, para aumentar o efeito preventivo da colonoscopia é também importante detetar mais eficazmente as LSS.

Tendo estes aspetos em consideração, os trabalhos aqui apresentados foram desenvolvidos para a melhoria da investigação em qualidade em colonoscopia de rastreio. No total, foram realizados um inquérito nacional, dois estudos observacionais e três ensaios randomizados, que pretenderam avaliar diferentes aspetos da qualidade e segurança em colonoscopia.

O papel da sedação em Gastrenterologia

Em primeiro lugar, o papel da sedação como aspeto fundamental da segurança e qualidade em colonoscopia foi explorado através de um inquérito nacional. Este inquérito versou sobre as práticas comuns envolvendo a sedação e monitorização nas unidades de endoscopia Portuguesas (no sector público e privado). Verificámos que a sedação é prática habitual na realização de colonoscopias, sendo o propofol e o midazolam os fármacos mais frequentemente utilizados. Embora o propofol seja o

fármaco de eleição para a maioria dos endoscopistas, este é quase exclusivamente utilizado por médicos Anestesiologistas.

Posteriormente e, motivados pelo diferente manejo no que respeita a sedação entre países europeus, realizámos um ensaio clínico de não inferioridade, controlado e randomizado, comparando a segurança e qualidade da sedação com propofol, administrado por médico não Anestesiologista (grupo A) e por médico Anestesiologista (grupo B) em doentes de baixo risco submetidos a colonoscopia eletiva em Portugal. Foram incluídas 277 colonoscopias (150 no grupo A e 127 no grupo B), não se verificando diferenças nos *endpoints* primários entre os dois grupos. A incidência de eventos adversos foi de 39.3% no grupo da sedação com propofol administrado por não anestesiologista e 39% no grupo da sedação por anestesiologista (diferença absoluta -0.3%, IC 95% -12.0 to 11.4%; p=0.959). Não se verificaram diferenças estatisticamente significativas nos principais indicadores de qualidade. A taxa de deteção de adenomas (ADR) foi de 28.4% no grupo A e 23.2% no grupo B (p=0.331). Assim, concluímos que a sedação com propofol administrado por médico não Anestesiologista não foi inferior à sedação por Anestesiologista numa população de baixo risco (ASA I-II) submetida a colonoscopia. Os eventos adversos foram comuns, mas podem ser manejados com segurança por uma equipa treinada para o efeito. A elevada qualidade da sedação com propofol traduziu-se ainda em maiores níveis de satisfação dos doentes e de vontade em repetir colonoscopia.

Indicadores de qualidade em colonoscopia

No sentido de avaliar a qualidade da colonoscopia da nossa unidade de técnicas (Hospital Beatriz Ângelo), foram medidos os indicadores de qualidade atualmente aceites, através de estudo transversal observacional. A taxa de deteção de adenomas foi de 36% (IC 95% 32-39), o número médio de adenomas por colonoscopia foi 0.66 (IC 95% 0.56-0.77) e a taxa de deteção de LSS foi de 1% (IC 95% 0-2). A taxa de entubação cecal ajustada foi de 93.7% (IC 95% 91.7-95.8). A maioria das colonoscopias foi realizada sob sedação profunda (53%) e em 35% não foi utilizada qualquer sedação. A utilização de sedação (com propofol ou midazolam) associou-se a uma taxa de entubação cecal mais elevada (OR 3.60, IC 95% 2.02-6.40, p < 0.001). Por um lado, a taxa de deteção de adenomas na nossa unidade foi superior à recomendada. Por outro lado, verificámos com elevada frequência inadequada preparação intestinal e reduzida taxa de deteção de LSS, pelo que foram instituídas medidas para melhorar ambos os indicadores.

Implementação de medidas para aumento da deteção de lesões pré-malignas

Com o intuito de determinar estratégias que contribuíssem para o aumento da deteção de lesões, nomeadamente LSS, foram desenhados dois estudos randomizados. Primeiramente, a utilidade do uso do *Endocuff* no aumento da deteção destas lesões foi avaliada através de um ensaio randomizado que incluiu 257 doentes submetidos a colonoscopia eletiva. Os doentes foram alocados aleatoriamente a um de dois grupos, consoante a colonoscopia fosse realizada com recurso a visão com *Endocuff* (VE) ou sem a sua utilização. O número de LSS por colonoscopia não foi significativamente superior no grupo com VE (0.233 vs 0.156, diferença média 0.076, p=0.381). Nenhum dos *endpoints* secundários, nomeadamente a taxa de deteção de adenomas (65.9% vs 66.4%; OR 0.977, IC 95% 0.583-1.638; p=0.931) ou de LSS (12.4% vs 7.8%; OR 1.671; IC 95% 0.728-3.836; p=0.226) foi superior no grupo EV. No nosso estudo, a utilização de VE não aumentou a taxa de LSS.

Em segundo lugar, realizámos um ensaio randomizado comparando o número médio de LSS e pólipos hiperplásicos com ≥10 mm detetados na retirada com NBI ou com luz branca. Foram também comparados a prevalência e as taxas de deteção de LSS, adenomas e pólipos. No total, 782 foram randomizados e o número médio de LSSs e pólipos hiperplásicos com ≥10 mm detetados por colonoscopia (endpoint primário) foi semelhante entre o grupo com NBI e com luz branca (0.118 vs 0.156, p=0.44). A taxa de deteção de adenomas (55.2% vs 53.2%, p=0.58) e LSS (6.8% vs 7.5%, p=0.502) não foi diferente entre os dois grupos. O tempo de retirada foi superior no grupo com NBI (10.88 vs 9.47 min, p=0.004), sendo o tempo de procedimento superior, no entanto, sem atingir significado estatístico (20.97 vs 19.30 min, p=0.052). Estes resultados demonstram que a utilização de NBI não aumenta a deteção de lesões serreadas ou de qualquer lesão pré-maligna, aumentando o tempo de retirada.

Por fim, decidimos explorar se a participação em projetos de investigação poderia ter impacto nos indicadores de qualidade das colonoscopias de rotina. Para tal, através de um estudo transversal, foi comparada a deteção de lesões pré-malignas em 147 colonoscopias eletivas aleatoriamente selecionadas e 294 colonoscopias de grupos controlo de dois estudos prospetivos. No grupo de investigação, verificou-se uma maior deteção de lesões pré-malignas (65.6% vs 44.2%, OR 2.411; IC 95% 1.608-3.614; p<0.001) e taxa de deteção de pólipos (73.8% vs 59.9%; OR 1.889; IC 95% 1.242-2.876; p=0.003), de adenomas (62.6% vs 44.2%; OR 2.110; IC 95% 1.411-3.155; p<0.001) e de LSS (17% vs 4.1%; OR 4.816; IC 95% 2.014-11.515; p<0.001). O número médio de lesões pré-

malignas (1.70 vs 1.06, p=0.002) e LSS (0.32 vs 0.06, p=0.001) por colonoscopia também superior no grupo de investigação. Numa análise multivariada ajustada para potenciais fatores confundidores, não houve diferença significativa em nenhum dos *outcomes*. Portanto, concluímos que os doentes envolvidos em ensaios clínicos podem beneficiar de exames com maior qualidade como demonstrado pelas taxas de deteção mais elevadas. Por conseguinte, o apoio das várias instituições no desenvolvimento da investigação clínica em colonoscopia pode resultar na melhoria qualidade em colonoscopia e da prevenção do CCR.

CHAPTER I.

INTRODUCTION

a. COLORECTAL CANCER

Colorectal cancer (CRC) is a leading cause of morbidity and mortality in the world. In Europe it is the second cause of newly diagnosed cancer with 519.820 cases and the second cause of cancer associated mortality with 244.824 deaths/year in 2020. In Portugal it is the leading cause of cancer with an incidence of 10.501 cases and the second cause of death with 4.320 deaths in 2020 [1]. The incidence has been increasing steadily in most countries with few exceptions, such as the USA and Germany[2], where it has been reduced in part due to screening and the removal of pre-malignant lesions[3,4]. The prognosis of CRC is highly variable with the 5-year overall survival ranging from over 90% in the early stages to 14% in advanced disease, however only 40% of cases are diagnosed as a localized disease [5].

In the last decades, knowledge regarding the pathogenesis, risk factors, pre-malignant lesion biology and cancer biology has evolved significantly and new patient tailored treatments are emerging. However, the importance of screening has a critical tool to fight the burden of this disease is as relevant as ever, mostly because most CRC cases develop after a long adenoma-carcinoma sequence which allows for the detection and removal of pre-malignant lesions.

Since the early stages of fiberoptic colonoscopy in the 60s the procedure has evolved significantly and is now at the center stage of CRC screening and it is endorsed by several scientific societies [6-9].

i. Epidemiology

The incidence of CRC and especially that of colon cancer is significantly different between regions and is highest in developed regions such as Japan, Australia, Europe and North America [1] as seen in figure 1. In Portugal the incidence is higher in the Northern region but the highest mortality is in Alentejo [10]. This variability may be explained not only by lifestyle and socioeconomic differences but also by healthcare (screening and treatment) access differences.

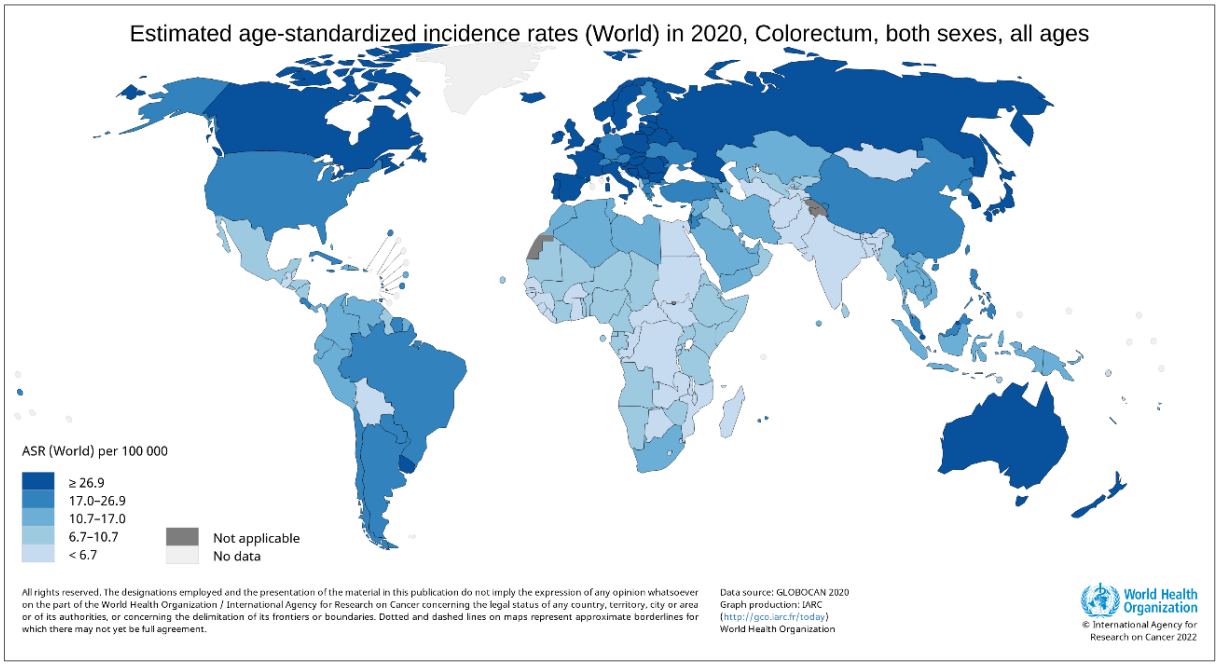

Figure 1. Estimated crude incidence rates of colorectal cancer in 2020. (World Health Organization, 2022)

In most countries, including Portugal, the incidence of CRC is still increasing but on the other hand, in countries such as the USA, the incidence has been declining for over 2 decades [2] with a 52% decrease in the mortality rate between 1970 and 2015, which has been attributed largely to screening but also to lifestyle changes, use of aspirin, hormone-replacement therapy and NSAIDs, less smoking and alcohol consumption and surgical and medical treatment advances.

Recently, the observation of a 2-fold increase in incidence rates in younger patients, aged 20-49 years [11], has led to a decrease in the screening threshold for average-risk individuals from 50 to 45 years in the ACS and followed by the ACG guidelines [8,9].

Globally, the incidence of colon and rectal cancer is estimated to increase by 60 and 71.5% until 2035, respectively [12].

ii. Etiology

A large body of evidence has emerged trying to identify the reasons behind a high regional variability of CRC incidence. Observational data show an association between diet and lifestyle and the development of CRC with a significant proportion being attributed to modifiable risk factors [13].

Increasing age is a major risk factor for CRC and even though the incidence has been increasing in those under 50, over 90% of the cases are diagnosed after 50 years of age.

In 2015 a WHO taskforce labeled red meat as “probably carcinogenic” based on a meta-analysis of cohort studies that showed that 100 g of red meat or 50 g of processed meat increase the risk of CRC by 15-20% [14]. Although it is challenging to identify with certainty the individual dietary risk factors it seems that a diet with a high intake of milk and dairy, fiber (fruits, vegetables, wholegrains and nuts) and fish is associated with a protective effect, whereas the consumption of alcohol, high fat meals, red meat, processed meat, sugar sweetened beverages, desserts and potatoes convey an increased risk of CRC [15]. The microbiome and the interplay with the diet and immunity has also been implicated in the pathogenesis of CRC [16]. Several micronutrients have been implicated in CRC carcinogenesis and while the evidence quality is weak, there seems to be a protective role of some micronutrients such as calcium, vitamin D, folic acid, magnesium and multivitamins [17].

Obesity and a high waist circumference have been shown to be important risk factors for men and women, while physical activity, especially vigorous activity, is associated with a decreased risk of CRC, especially in men [18].

Several drugs have been evaluated for their potential as chemoprophylactic agents. Two of the most studied agents are aspirin and non-steroidal anti-inflammatory agents (NSAIDs). Aspirin has been studied in observational and randomized trials and 6 meta-analyses have pooled the data and confirmed a protective role (RR from 0.71 to 0.86). NSAIDs also seem to have a beneficial effect but they have only been studied in observational studies which have been pooled in 3 meta-analyses [17]. However, these agents are not without adverse effects and currently only aspirin may be considered in adults aged 50-59 and with a cardiovascular risk over 10%, as recommended by the US Preventive Services Taskforce.

Environmental and dietary exposures and pharmacologic interventions affect the risk of CRC but their precise roles remain elusive. Furthermore, different molecular subtypes of CRC (and precursor lesions) seem to have different risk factors which increases the complexity of these relations.

iii. Biology

Colorectal cancer is the result of a multi-hit process involving the individual genetic background and the exposure of the colonic epithelial cells to specific carcinogens over time [19].

Tumor cells require an accumulation of methylation abnormalities and genetic and epigenetic events that lead to uncontrolled cell proliferation and the evolution to adenoma and carcinoma. These can be the gain of function of proto-oncogenes or the loss of function in tumor suppressor genes.

Most cases of sporadic CRC develop through one of two major pathways: the chromosome instability pathway (non-hypermutated - less than 8.26 mutations per 10^6 bases) in 86% and the MSI-H - microsatellite instability pathway (hypermutated – more than 12 mutations per 10^6 bases) in 14% of cases [20]. Several genes like *APC* and *TP53* (tumor suppressor genes) and *KRAS*, *PI3KCA*, *BRAF* and *NRAS* (oncogenes) are frequently involved in both pathways.

The CIN pathway is associated with the classic pre-malignant lesion, the tubular adenoma and the tumorigenesis of these lesions may take over 10 years. The CIMP/MSI-H is associated with serrated lesions and presents a much shorter carcinogenesis timeframe.

These classifications relate not only to different neoplastic origin and progression but they also have prognostic implications.

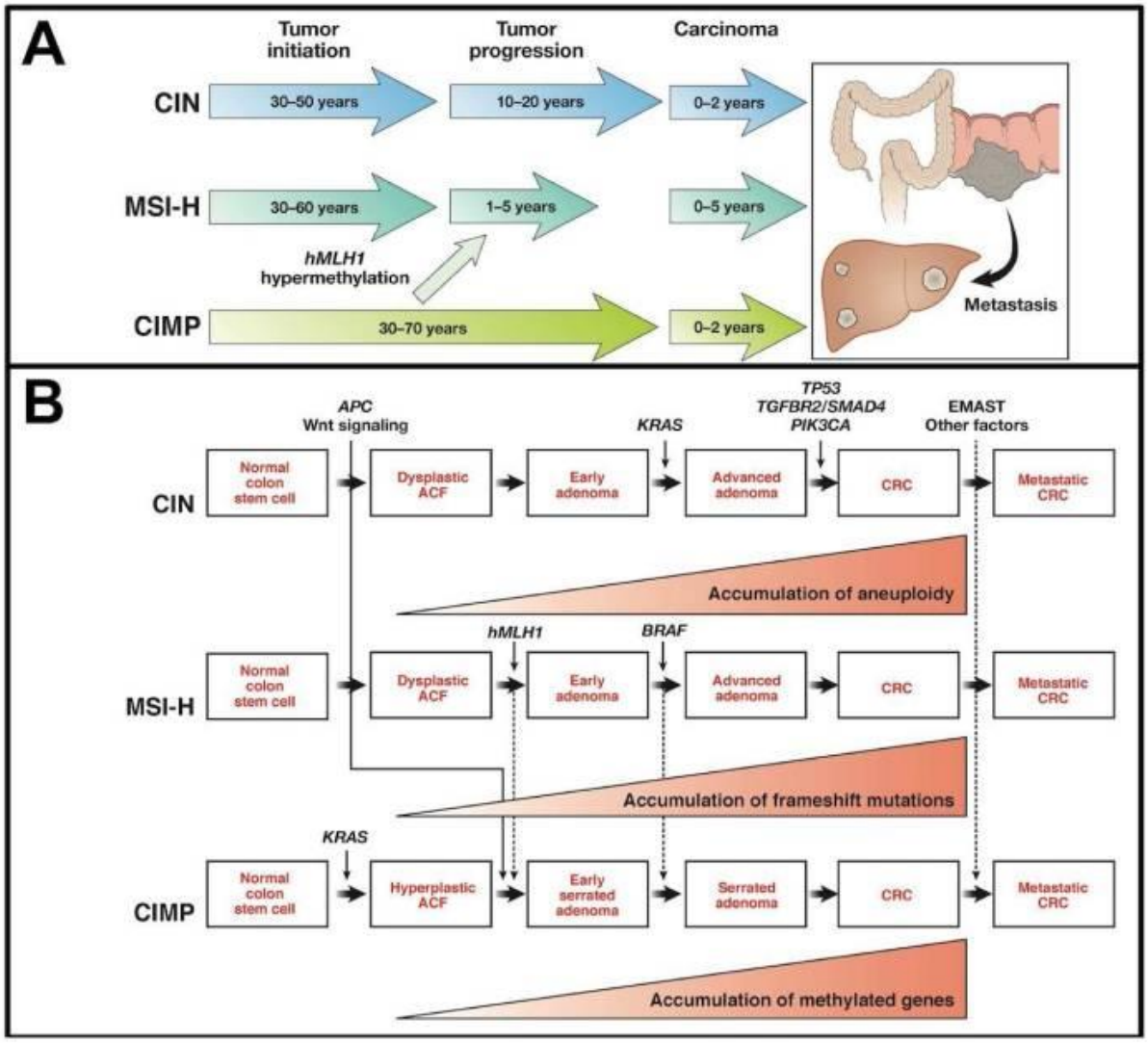

Figure 2. Models and timelines of colorectal cancer pathogenesis according to the pathway marked by chromosomal instability (CIN), microsatellite instability (MSI-H) and CpG island methylator phenotype (CIMP). (adapted from Carethers JM, Jung BH. Genetic and genetic biomarkers in sporadic colorectal cancer. Gastroenterology 2015; 149: 1177-90)

Pre-malignant lesions

Most cases of colorectal cancer are originated in pre-malignant lesions which present themselves in two major classes: the conventional adenoma and the serrated class lesion.

Sporadic CRC is thought to originate from Wnt signaling hyperactivation that leads to cellular overgrowth and the formation of dysplastic focus (adenoma precursor). Sequential alterations through the CIN pathway lead to the progression of the adenomas to increasingly dysplastic lesions and ultimately to invasive carcinomas. Serrated lesions arise from the activation of BRAF which may then lead to MSI-H tumors and sessile serrated lesions or they can acquire TP53 mutations and Wnt overactivation and lead to traditional serrated adenoma, a MSS tumor.

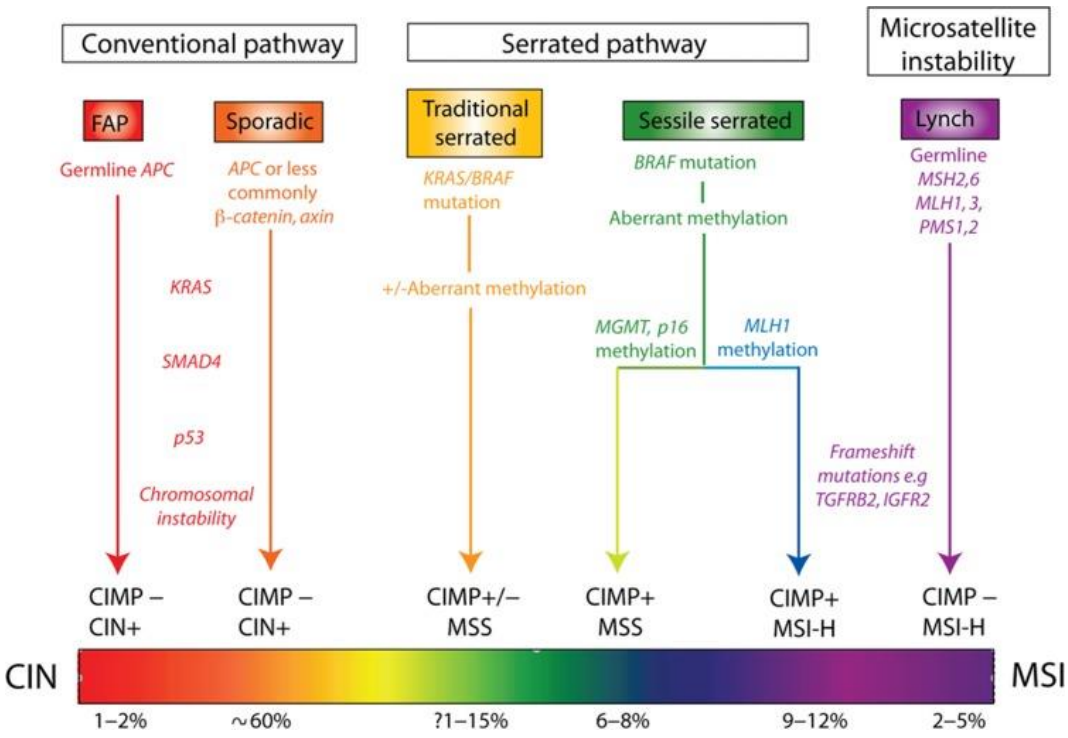

Figure 3. Pathways of Colorectal Carcinogenesis – conventional adenomas progress by the chromosomal instability pathway. The serrated pathway is initiated by *BRAF* or *KRAS* mutation and methylation of tumor suppressing genes (CIMP). FAP, familial adenomatous polyposis. Initiation occurs though the activation of Wnt pathway of BRAF mutation (serratated pathway). (adapted from East JE et al. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. Gut 2017; 66(7), 1181–1196)

Conventional Adenoma

Conventional adenomas are the classical pre-malignant lesions, they evolve over 10-20 years through the CIN molecular pathway and their carcinogenic potential is well established. These lesions are highly prevalent being present in half of the persons over 50 years old[21]. They are more frequently found in the proximal colon in persons older than 60 years old and in the distal colon in younger individuals. Their morphology may be flat, sessile or pedunculated, with a short or a long stalk.

With time, adenomas become progressively larger, dysplastic and malignant. The risk of malignancy is higher in large lesions; hence they are classified according to their size into diminutive (<6 mm), small (6-10 mm) or large (>10 mm). The risk of a sub centimeter lesion to be malignant is less than 1%. Large adenomas or small/diminutive adenomas with a villous component (25%) or high-grade dysplasia are considered to be an advanced neoplasia.

Sessile Serrated Class

Sessile serrated lesions are distinct from conventional adenomas. The WHO subclassifies serrated lesions into: hyperplastic polyp (HP), sessile serrated adenoma/polyp (SSA/P) and traditional serrated adenoma (TSA). However, the name SSA/P may be misleading since most sessile serrated polyps are not polypoid and have no cytological dysplasia, unlike adenomas [22]. As such we will address these lesions as Sessile Serrated Lesions (SSL) as proposed by the British Society of Gastroenterology [23]. SSL may be further divided according to the presence or absence of cytological dysplasia.

Hyperplastic polyps present straight crypts with little distortion, they are typical wide and "serrated" at the surface and can be divided into microvesicular (MVHP), goblet cell and mucin poor types according to the characteristics of the epithelium.

Traditional Serrated Adenomas are rare dysplastic polypoid lesions with villiform histology. They have similarities with conventional tubulovillous adenomas but present an eosinophilic cytoplasm and crypt building. The molecular features include *KRAS* or *BRAF* mutations and variable levels of CIMP positivity [23]. They are usually found in the distal colon.

Sessile serrated lesions are characterized by disorganized and distorted T or L-shaped crypt growth which may appear dilated with excessive "serration" at the basal third and present with inverted crypts [23]. They frequently produce excessive extracellular mucin which fills dilated crypts and coats the lesion. These lesions are preferentially located on the proximal colon, they are more difficult to detect than adenomas because of their flat morphology, cloud-like appearance, the tendency to harbor a mucus cap and indistinct edges [24]. Risk factors for SSL have been studied and include smoking, higher BMI and female sex [25].

Their prevalence may be as high as 22% in a screening population but the reported detection during colonoscopy is highly variable ranging from 1-18% in one American center [26] and 6-22% in two centers in the Netherlands [27]. This may be due not only to their endoscopic appearance which makes them harder to detect, with higher miss rates when comparing to adenomas [28] but also due to a lack of pathology awareness as some pathologists fail to identify SSL, as shown in a study from 32 centers in the US and Germany [29].

The risk of malignant development from these lesions is less well established than adenomas but they are believed to be the result of a specific carcinogenesis pathway

involving BRAF mutation and CPG island methylation and to have a faster development when compared to traditional adenomas. Serrated lesions are thought to be precursors to 20-30% of all CRC [30], especially after a screening colonoscopy. Hence, sessile serrated lesions pose relevant detection and management issues.

b. SCREENING

According to the WHO, screening refers to the application of a test in a population with no signs or symptoms of the disease in order to identify individuals at risk for early disease and to allow early diagnosis and more effective treatment.

CRC is currently considered a preventable disease, since it has been shown that screening and surveillance are effective in reducing both the incidence and the mortality [4,31-34]. This reduction has been identified over the last few decades [2] and it is mainly attributed to the effect of screening and the removal of early superficial neoplastic lesions [35,36].

Screening is currently endorsed by many organizations [8,9,37-39] but only a few countries have organized population screening programs and most perform opportunistic screening with any of the available tests. In Europe, there is a 450-page document with 90 authors from 32 countries published in 2010 and summarized in 2013 - The European Guidelines for Quality Assurance in Colorectal Screening and Diagnosis[39], that provides an evidence-based review of existing data on CRC screening that stresses quality measures and cost-effectiveness.

There are several screening options currently available: stool-based tests (guaiac, immunochemical tests and stool DNA) and optical colonoscopy (first tier), sigmoidoscopy and CT colonography (second tier) and capsule colonoscopy (third tier) [40]. All of these tests are approved for screening with their own specific advantages and disadvantages, but colonoscopy is the only “one step” procedure as all the others require a colonoscopy if positive (2-step approach). Individuals should be stratified according to their relative risk for CRC and for those with an average risk screening can be done with any chosen strategy and it is generally recommended for individuals aged 50-75 but recently, the US Multi-Society Task Force, which represents the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy have recommended to begin screening for average-risk individuals at age 45.

i. Stool-based tests

A large body of evidence supports the effectiveness of fecal occult blood testing. Guaiac tests (gFOBT) are the oldest and although effective, they have several caveats that decrease their accuracy, such as fecal hydration level, the byproducts of certain foods (red meat, broccoli, cauliflower) and the amount of hemoglobin degradation caused by normal metabolism. gFOBT has been shown to decrease CRC associated mortality by 15-33% in the short-term but not all cause mortality in the long-term in large randomized trials [32,41]. Immunochemical (FIT) tests represent an improvement over guaiac tests in both sensitivity and specificity for CRC and adenomas [42] and it is likely to replace them in most instances. When using the manufacturer threshold (20 μg hemoglobin per gram of stool), the pooled sensitivity for detection of colorectal cancer was 0.74 (95% CI, 0.64-0.83; 9 studies; n = 34 352) and the pooled specificity was 0.94 (95% CI, 0.93-0.96; 9 studies; n = 34 352)[43]. In both cases, follow up should be done with a colonoscopy after a positive result and another stool test in 1-2 years in case of a negative one.

Stool DNA tests are a recent stool test alternative with improved sensitivity to detect adenomas and cancer but with a higher rate of false positives[44]. The long-term effect on CRC incidence and mortality is still unknown and the repeat interval has been suggested to be every 1-3 years [8,43].

CT colonography

Virtual colonoscopy or CTC is performed using standard CT equipment and a dedicated software to render 3D images of the colon. CTC is a screening option and the proposed repeat interval is 5 years [8,9,40].

Several studies have investigated the diagnostic performance of CTC when compared to optical colonoscopy [45-47]. More recently, CTC was also compared to capsule endoscopy and it was inferior for the detection of small (<10 mm) lesions [48]. In a meta-analysis including 49 studies and 11.151 patients the sensitivity of CTC for CRC was 96.1% (398 of 414; 95%CI 93.8% to 97.7%) but when both cathartic and tagging agents were used no cancer was missed [49]. Unfortunately, the sensitivity is lower for small lesions and especially for flat lesions like SSLs.

CTC is a moderately expensive, high sensitivity (for CRC detection), low-risk procedure which carries the exposure of a small amount of ionizing radiation and the burden of possible extra-colonic incidental findings.

Capsule colonoscopy

Capsule colonoscopy is a non-invasive diagnostic procedure where the patient ingests a small video capsule after a cathartic bowel preparation. It is FDA approved for patients after an incomplete colonoscopy and those who are not candidates for optical colonoscopy. It is considered a third-tier test by the US Multi-Society Taskforce and should be used with a 5-year interval.

CC performance has improved with newer generation equipment with a sensitivity over 80% and a specificity of 93% for lesions >5 mm [50,51]. In the most recent RCT CC outperformed CTC for lesions 6-9mm [48].

Flexible sigmoidoscopy

Flexible sigmoidoscopy allows the direct visualization of the distal colon and rectum and if an adenoma is found a full colonoscopy is to be performed. A negative procedure should be followed up in 5 years [8,37,38,43].

Sigmoidoscopy role in screening has been studied in four large RCTs in the UK, US, Italy and Norway that showed consistent reductions in both incidence and mortality with a once or twice in a lifetime sigmoidoscopy [52-55]. The pooled analysis of these four studies yielded a risk reduction for incidence (RR 0.76, 95%CI 0.70-0.83) and mortality (RR 0.74; 95% CI 0.69 to 0.80) [56].

Optical colonoscopy

Colonoscopy is possibly the most effective screening procedure and is considered a 1st tier method by the USMSTF [40]. Colonoscopy allows the direct visualization of the entire colon but is an invasive procedure with a small but non neglectable risk of complications. Colonoscopy is the only test that can be used as a stand-alone procedure for screening in average and increased risk populations, in diagnosis, in surveillance after polypectomy and is always necessary after a positive result with any of the other screening alternatives. Several large trials like the CONFIRM, COLONPREV and NordICC studies are ongoing and hopefully will determine the value of colonoscopy versus that of FIT. Currently we have large observational data to support colonoscopy as an effective intervention to reduce both CRC incidence and mortality. In the follow up of the classical National Polyp Study, a 53% reduction in CRC mortality after a median follow up of 15.8 years was observed [4]. In Ontario, Rabeneck followed

a large cohort for 14 years and reported a 3% reduction in the hazard risk of death for every 1% increase of the colonoscopy rate [57]. In the largest cohort study to date, the Nurses' Health Study, which included 88,902 participants over a 22 year period there was a 68% reduction in the risk of CRC mortality (HR 0.32, 95%CI 0.24 to 0.45)[33]. In this study, patients who developed CRC within 5 years of the colonoscopy were two times more likely to be characterized as CIMP of MSI-H. In the German population-based case-control study Brenner et al reported a 91% decrease in the risk of CRC[58] and when pooling 6 large observation studies under a meta-analysis there was a 69% risk reduction in the overall incidence and 68% in mortality and the protective effect was also present for proximal cancer [59].

These data strongly suggest that colonoscopy is probably more effective than sigmoidoscopy in reducing both the incidence and mortality in the distal, albeit less so in the proximal colon.

Unfortunately, not all colonoscopies are equal. Since the late nineties that it is known that colonoscopy is far from perfect with a significant proportion of missed lesions reported in the well-known tandem study by Douglas Rex in 1997 [60]. Since then, several important studies have confirmed this limitation and addressed what is known to be the inter-endoscopist variability and its' impact in future CRC risk. In a seminal work by Zauber and colleagues at Kaiser Permanente in California, they analysed 314,872 colonoscopies from 136 gastroenterologists and observed adenoma detection rates as low as 7.4 and as high as 52.5%. They identified an inverse relationship between detection rates and the risk of CRC and death from CRC in the following 10 years. For every 1% increase in the ADR there was a 3% decrease in the risk of CRC [35]. This effectiveness measure has been highlighted in a prospective cohort of 146,860 colonoscopies performed by 294 endoscopists in Poland where it was seen not only that being a high detector reduces the risk of cancer and death but also that endoscopists were able to improve their detection rates over time and that this improvement is also associated with a lower CRC risk [61].

This variability can be the result of factors such as equipment, colonoscopy technique, bowel preparation, withdrawal time or even endoscopist sleep deprivation [62-64].

Since it has become evident that colonoscopy is critical for successful CRC screening and its' effectiveness is highly variable and operator dependent, many societies have been working to identify key colonoscopy performance/quality measures [65-68]. Most societies and experts agree that the adenoma detection rate is a surrogate for meticulous inspection of the colonic mucosa and currently it is the best quality

surrogate for colonoscopy, since a higher ADR result in a smaller risk of interval CRC, advanced stage CRC and mortality. Still, this indicator has some limitations. The most obvious one is that the number of adenomas per patient is not included in this indicator which may lead to the "one and done" effect, however this seems to be fairly uncommon, affecting only around 7% of endoscopists[69]. Another limitation is that ADR is not affected by the detection of sessile serrated lesions, which are important lesions thought to be an important precursor of interval cancer, especially on the right colon [33]. It seems however that the ADR is correlated to the SSL detection rate [70], which is a possible explanation of its' ability to predict interval cancer even if serrated lesions and not adenomas are the precursor of many of these cancers.

The detection of pre-malignant lesions is therefore the major outcome to strive for when performing a colonoscopy and an increase in the sensitivity for such lesions may have a significant impact in decreasing the incidence of interval cancer rates, leading to a decrease in CRC mortality.

Several techniques have been developed with the aim of improving the adenoma detection rate. These include improving the bowel preparation, patient sedation, endoscopic maneuvers, high-definition imaging, magnification and chromoendoscopy techniques, as well the use of caps, distal attachment devices and wide-view endoscopes. Still, the available data for each technique is not unequivocal of their effectiveness for the detection of adenomas and even less so for sessile serrated lesions.

Narrow band imaging (NBI) is an Olympus™ proprietary technology that has been studied with equivocal results for the detection of adenomas in several trials [71-73] but due a technological improvement in last NBI generation, there was a higher ADR with NBI when compared to white light in a recent meta-analysis [74]. NBI has also been to shown to be effective for SSL detection, but only in one trial performed in a single academic center and in a specific syndrome called sessile serrated polyposis [72,75]. In a randomized controlled trial (RCT) comparing NBI (Olympus™ 190 series colonoscopes) and high definition - white light (HD-WL) colonoscopy for serrated lesions proximal to the sigmoid colon in average risk individuals and showed a trend towards higher detection in the NBI but failed to achieve statistical significance for the primary endpoint (number of proximal serrated lesions) [76]. Therefore, it's still unsettled whether NBI should be used systematically during colonoscopy to increase detection of CRC precursor lesions.

Apart from the detection of pre-malignant lesions there are several other aspects important enough to deserve their own quality indicators. These aspects can be divided into pre-procedure (indication, bowel preparation, informed consent), intra-procedure (cecal intubation rate, polyp detection rate, withdrawal time, polypectomy technique, polyp retrieval rate, tattooing, advanced imaging assessment, complications, monitoring and sedation documentation and patient experience) and post-procedure (appropriate surveillance) indicators which are also important on their own.

ii. Procedural sedation

GI endoscopies are invasive, unpleasant and sometimes painful experiences. To overcome such unpleasantness, we have been searching for ways to minimize it since the introduction of the fiberscope in the 50's.

Sedation is a fundamental aspect of gastrointestinal (GI) endoscopy. Although some patients can perform diagnostic esophagogastroduodenoscopy (EGD) and colonoscopy without sedation, the use of sedation is associated with a higher patient satisfaction [77,78] and procedural quality [79]. There is also an increasing demand for sedation by the patients and failure to do so may hamper the efforts of an effective screening strategy.

There are several options for sedation which range from light sedation (anxiolysis) to general anesthesia depending on the procedure being performed, the center expertise and the individual patient. Still, the most commonly used sedation is moderate-deep sedation achieved by midazolam with or without an opioid (meperidine / pethidine, fentanyl or alfentanyl), which is commonly designated as "traditional sedation", with the other option being propofol which can also be used alone or in combination with analgesic opioids or midazolam.

The technological advances in endoscopy have improved the diagnostic and therapeutic capabilities but they have also allowed for faster and less painful examinations. Advances like the utilization of thinner endoscopes [80], variable stiffness colonoscopes [81], CO_2 insufflation [82] and water immersion colonoscopy [83] allow for less painful procedures. Although helpful, these options are probably not as effective as medical sedation has been shown to be.

There has been a continuous evolution on sedation practices for endoscopy since the early 60's when pentobarbital use was described in conjunction with a transtracheal

xylocaine injection [84]. The use of meperidine as an analgesic was an initial strategy and it was followed by the widespread adoption of the combination with diazepam, which was shown to improve the rate of "satisfactory examinations" by 20% comparing to meperidine alone [85]. This set the rationale for the so-called traditional sedation.

After almost two decades there was the advent of midazolam [86]. Midazolam had a very good acceptance in the endoscopy community in virtue of its faster induction time, higher effectiveness and shorter duration of action comparing to diazepam while keeping the safety feeling provided by the existence of a reversal agent. However, there were several (71) death reports in the 80's with midazolam-based sedation and the Food and Drug Administration (FDA) issued a warning on this topic. Later, a more systematic epidemiological approach, led by a joint effort from the FDA and the American Society of Gastrointestinal Endoscopy (ASGE), failed to show an increased risk of death with midazolam compared with diazepam [87]. At the present time, midazolam is considered a safe agent and is commonly used as a sedative in gastrointestinal endoscopy.

Propofol, an ultra-short acting hypnotic agent, was introduced a few years after midazolam [88] but it had a much slower uptake due to its use mostly as an anesthetic agent and as a sedative for critically ill patients and its' product label states that it "should be administered by persons with training in general anesthesia" in the USA and by anesthetists and intensive care physicians in some European countries. Because of this, most endoscopists feel untrained to administer propofol. Still, from a pharmacokinetic/pharmacodynamic point of view, propofol is superior to midazolam as it has a faster onset and a shorter predictable duration of action [89]. Propofol has since been proved to be a better sedative for endoscopy when compared to traditional sedation, improving both patient and endoscopist satisfaction, procedural quality indicators (such as cecal intubation time), induction, wake up and psychomotor recovery times [77,78,90-92]. These improvements are achieved without an increased risk for adverse events as shown in several meta-analyses of randomized controlled trials (RCT) [77,78,93]. These characteristics may have significant impact in procedural quality, patients' acceptance (especially for screening procedures) and endoscopic unit productivity.

One important concern regarding sedation in colonoscopy is the theoretical increase in perforation risk. In two observational but robust population-based studies in the US it has been shown that propofol sedation is not associated with an increased

perforation risk [94,95]. It may, however, be associated with a slightly higher risk for aspiration pneumonia [95]. Another recent observational study showed an increased risk for perforation but only in therapeutic colonoscopy and when adjusted for confounders the odds ratio was 1.34 with a p value of 0.04 [96]. Obviously, it is hard to detect small effect sizes for rare outcomes such as colonic perforation, but so far, the available evidence suggest that sedation doesn't play a significant role in perforation rates.

Despite the advantages of propofol and the endorsement of propofol sedation by several national and international societies [97-101], it is still underused in most settings, because of medico-legal aspects, namely the requirement of an anesthesiologist and, consequently, increased costs [102].

The non-availability of NAAP seems to be a limiting step for the availability of propofol sedation and it significantly increases costs in a non-reasonable tradeoff. This has been shown in a cost-effectiveness analysis by Cesare Hassan, with a calculated cost of 1.5 million USD/life year gained [103].

There is wide variability in sedation practice worldwide. In the USA the number of endoscopic procedures in increasing [104], as a result of the increased uptake of colorectal cancer screening colonoscopy. The participation of anesthesiologists in endoscopy has doubled from 14% in 2003 to 30% in 2009 [105] and it was expected to pass the 50% mark by 2015 [106]. On the other hand, non-anesthesiologist administration of propofol (NAAP) is becoming less common, as a result of Medicare reimbursement change in 2009 [107], although this policy has been rejected by several states.

In Europe the variability is even wider. In most countries routine diagnostic EGDs are performed without sedation [108] with colonoscopies being more likely to receive some form of sedation [102]. The countries with highest rates of propofol sedation are probably Switzerland [109] and Germany [110] with high rates of NAAP. In the latter, over 90% of the colonoscopies are performed with sedation, 97% of them with propofol and only 2% of those with support of an anesthesiologist. These data were acquired from a German national survey in 2011 with 732 respondents and showed an increase in sedation and propofol rates comparing to the first survey, 4 years earlier.

NAAP is also a common practice in Denmark, Austria, Spain, Italy, Greece, the Netherlands and Sweden [101,111-114].

When comparing propofol to traditional sedation there is high quality evidence, which includes several RCTs and five systematic reviews (4 of them with meta-analysis - table 1) [77,78,90,92,93].

Table 1. Meta-analysis of randomized controlled trials of propofol versus traditional sedation in endoscopy. (adapted from Ferreira AO, Cravo M. Sedation in gastrointestinal endoscopy: Where are we at in 2014? World J Gastrointest Endosc. 2015; 16(2): 102-9)

Study	Procedures	Sedation compared	Number of studies (cases)	OR (95% CI) for adverse events
Qadeer MA et al, 2005	EGD/colonoscopy/ ERCP/EUS	Propofol vs. traditional sedation	12 (1161)	0.74 (0.44-1.24)
Singh H et al, 2008	Colonoscopy	Propofol vs. traditional sedation	22	Hypoxia: 0.69 (0.25-1.89); Hypotension: 1.03 (0.28-3.83)
Bo LL et al, 2011	ERCP	Propofol vs. traditional sedation	6 (663)	1.69 (0.82-3.50)
Garewal D et al, 2012	ERCP	Propofol vs. traditional sedation	4 (510)	narrative
Wang D et al 2013	EGD/colonoscopy/ ERCP	Propofol vs. traditional sedation	22 (1798)	0.90 (0.70-1.17)

The results are very consistent in showing a similar rate of adverse events with propofol versus traditional sedation. The advantages of propofol are shorter recovery and discharge periods, higher post-anesthesia recovery scores, better sedation, and greater patient cooperation. One limitation of the majority of the RCTs included in the meta-analysis is the lack of anesthesiologist participation. This may limit the generalizability of the data but it's unlikely that there would be a decrease in the safety or quality of this sedation when performed by an anesthesiologist.

The big question is therefore who should be responsible for the administration of propofol [115].

To address this issue there is only one RCT [116]. This study by Poincloux et al randomized 90 low risk patients undergoing colonoscopy for sedation by an anesthesiologist using a target control infusion (TCI) or by the endoscopist using a modified patient-controlled sedation pedal. In this study patients who were sedated by anesthesiologists had more frequent side events (16% vs 3%; p=0.008), had higher doses of propofol (94 vs 260 mg), less pain but similar satisfaction levels.

Apart from randomized controlled trials, there's significant experience with NAAP and extensive prospective evaluation on the safety and effectiveness of this type of sedation, especially for low-risk patients. Rex et al published in 2009 a sum of all

published evidence on NAAP and collected unpublished prospective and retrospective records from several centers all around the world, totaling 646 080 cases out of which 4 patients died and 11 were intubated. These numbers are not very different from published mortality rates for general anesthesia which is 1:13,322 (overall) and 1:200,200 in ASA I-II [117]. More recently, a large German experience of 24 441 cases on propofol and propofol with midazolam has been published[118]. The data was collected prospectively and severe adverse events were reported in only 4 patients, with no severe outcomes (death or permanent neurologic damage).

Guidelines

As a consequence of the advantages provided by propofol sedation and the difficulty in adopting its use due to logistical, financial and medico-legal issues, several national and international guidelines have been published in the last decade and are shown in table 2 [97-101,114,119,120]. These guidelines help to provide the framework to allow endoscopists to perform NAAP in their countries.

Table 2. Existing societal guidelines for non-anesthesiologist administration of propofol (NAAP). (adapted from Ferreira AO, Cravo M. Sedation in gastrointestinal endoscopy: Where are we at in 2014? World J Gastrointest Endosc. 2015; 16(2): 102-9)

Scientific Society	Limitations	Consider anesthesiologist
Sociedad Española de Endoscopia Digestiva (SEED), 2020	Complex procedure; ASA III	ASA≥ III; long/complex procedure; difficult airway
Canadian Association of Gastroenterology (CAG), 2008	n/a	ASA≥ III; long/complex procedure; difficult airway
German S3 guidelines - DGVS/DGAI, 2008	ASA≥ III; long/complex procedure; difficult airway	ASA≥ IV; long/complex procedure; difficult airway
European Society of Gastrointestinal Endoscopy (ESGE/ESGENA), 2010/2013	n/a	ASA≥ III; long/complex procedure; difficult airway
American Society of GI Endoscopy - ASGE, 2018	n/a	ASA≥ III; long/complex procedure; difficult airway

Of note, the German guidelines were the result of a collaboration between the GI endoscopy and anesthesia national societies and are therefore a valuable evidence-based consensus document made by the country that probably has more frequent propofol sedation in endoscopy in the world.

In summary, sedation is a fundamental part of gastrointestinal endoscopy. Sedation should be tailored to the patient and the procedure being performed with the aims of keeping both comfort and safety. Endoscopy teams should be composed of medical practitioners and nurses competent in the endoscopic procedures and in sedation and monitoring.

These studies aim to improve the screening effect on CRC incidence by increasing procedural quality and public awareness, as well as stimulating clinical research in endoscopy.

c. RESEARCH QUESTIONS AND AIMS

- Research question 1

What are the current practices regarding sedation and monitoring in gastrointestinal endoscopy in Portugal?

Aim

To evaluate the current sedation and monitoring practices in Portuguese endoscopy units (both in the public and private practice) and the opinion of Portuguese endoscopists regarding non-anesthesiologist administration of propofol (NAAP).

- Research question 2

Is NAAP effective and safe in routine colonoscopy of low-risk patients in a Portuguese hospital?

Aim

To compare the safety and effectiveness of NAAP and anesthesiologist directed sedation safety, in low-risk patients undergoing routine colonoscopy in Portugal.

- Research question 3

How effective are the colonoscopies performed in a public non-tertiary hospital (Hospital Beatriz Ângelo) and how do they compare to the currently accepted quality indicators?

Aim

To evaluate the quality of colonoscopy at Hospital Beatriz Ângelo in Loures, Portugal, in the first 3 years since its opening in 2012 having as comparators the established indicator thresholds.

- Research question 4

Is there an increase in the detection of sessile serrated lesions with the systematic use of Endocuff Vision in colonoscopy?

Aim

To evaluate the effect of Endocuff-assisted colonoscopy on SSL detection and the detection of serrated lesions at least 10 mm in size

- Research question 5

What is the effect of the systematic use of NBI during colonoscopy withdrawal on sessile serrated lesions detection?

Aim

To evaluate if the systematic usage of NBI during colonoscopy withdrawal contributes to a higher rate of SSL detection in an average CRC risk population.

- Research question 6

Is there a difference in colonoscopy quality indicators between routine colonoscopy and colonoscopies performed in the setting of a prospective research study?

Aim

To assess the colonoscopy quality indicators in patients who were included in a control group for an endoscopic clinical trial at our institution and compare them with a sample group from the same institution.

CHAPTER II.

SEDATION IN ENDOSCOPY

a. ENDOSCOPIC SEDATION AND MONITORING PRACTICES IN PORTUGAL: A NATIONWIDE WEB-BASED SURVEY

Alexandre Oliveira Ferreira, Joana Torres, Mário Dinis-Ribeiro, Marília Cravo

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Endoscopic sedation and monitoring practices in Portugal: a nationwide web-based survey

Alexandre O. Ferreira[a,b], Joana Torres[b], Mário Dinis-Ribeiro[c] and Marília Cravo[b]

Background National surveys have been used to obtain information on sedation and monitoring practices in endoscopy in several countries.

Aims To provide data from Portugal and query the Portuguese endoscopists on nonanesthesiologist administration of propofol.

Materials and methods A 31-item web survey was sent to all 490 members of the Portuguese Society of Gastroenterology.

Results A total of 129 members (26%) completed the questionnaire; 57% worked in both public and private practice. Most performed esophagogastroduodenoscopy without sedation (public – 70%; private – 57%) and colonoscopies with sedation (public – 64%; private – 69%). Propofol was the most commonly used agent for colonoscopy, especially in private practice (52 vs. 33%), and it provided the best satisfaction (mean 9.6/10). A total of 94% chose propofol as the preferred sedation for routine colonoscopy. Nonanesthesiologist administration of propofol was performed only by four respondents; however, 71% reported that they would consider its use, given adequate training. Pulse oximetry is monitored routinely (99%); oxygen supplementation is administered by 81% with propofol and 42% with traditional sedation. Most (82%) believed that propofol sedation may increase the uptake of endoscopic screening for colorectal cancer.

Conclusion The use of sedation is routine practice in colonoscopy, but not esophagogastroduodenoscopy. The preferred agent is propofol and it is used almost exclusively by anesthesiologists. *Eur J Gastroenterol Hepatol* 27:265–270

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Keywords: endoscopic sedation, midazolam, nonanesthesiologist-administered propofol, propofol

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Introduction

Gastrointestinal sedation is becoming ubiquitous in several countries [1–7] because of the obvious advantage it represents for patients' comfort and satisfaction and also because it contributes toward increasing the quality of the procedures [8,9]. The best sedation modalities are still a topic of debate. Traditional sedation, consisting of the combination of a benzodiazepine and an opioid, is still very common, but it is becoming accepted that propofol-based sedation allows for the best trade-off in terms of safety and effectiveness, being endorsed by several national and international societies [10–15].

Nevertheless, sedation practices are very different between geographical locations; although data are available from the USA [6] and some European countries [1,3–5,7,16], in Portugal, little is known on sedation and monitoring practices and the last national guidelines on sedation were issued in 1997 by the Portuguese Society of Digestive Endoscopy.

This study aimed to evaluate the current sedation and monitoring practices in Portuguese endoscopy units (both in the public and in the private practice) and the opinion of Portuguese endoscopists on nonanesthesiologist administration of propofol (NAAP).

Materials and methods

A 31-item web survey (Supplementary Document 1) was developed by the authors using the *http//:www.survey monkey.com* website. The questionnaire was based on the German survey [4], but slightly modified, including specific work setting data from practitioners who work in both public and private practice (which is very common in Portugal and not usual in Germany) and the endoscopists' personal opinion on the impact of sedation in endoscopic screening adherence and sedation training during the gastroenterology residency.

The questionnaire included questions on demographic data, procedural volume, sedation and monitoring practices, personal preferences, and opinion on NAAP. Residents were identified and their survey did not include questions 5–20 as these were related to work setting and volume and personal practices (Supplementary Document 1) and

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most residents do not perform endoscopy autonomously. However, they were asked whether they would consider using NAAP in the future.

An introductory e-mail was sent in April 2014 by the Portuguese Society of Gastroenterology to all its 490 members. The e-mail included a cover letter stating the background and aims of the study and the link to the survey website. To increase the response rate, two e-mail reminders were sent 2 and 4 weeks later. Respondents were informed that their identity would be kept anonymous.

Statistical analysis

Data were exported and analyzed in SPSS Statistics 21 (IBM Corporation, Armonk, New York, United States). Continuous data were compared using Student's *t*-test and categorical variables were tested using a corrected χ^2-test.

Results

Demographics

A total of 171 members, out of 490 members, responded to the survey and 129 (26.3%) completed all questions. Demographic characteristics, workplace, and volume are shown in Table 1.

Combining individual performance in public and private practice, the median number of esophagogastroduodenoscopy (EGD) and colonoscopies was 60 and 85/month, respectively.

Sedative regimens

Figure 1 shows the sedation options used for EGD and colonoscopy in the public and the private setting. The endoscopists were asked to report the proportions of EGDs and colonoscopies performed with no sedation, traditional sedation, or propofol-based sedation, both in the public and in the private setting.

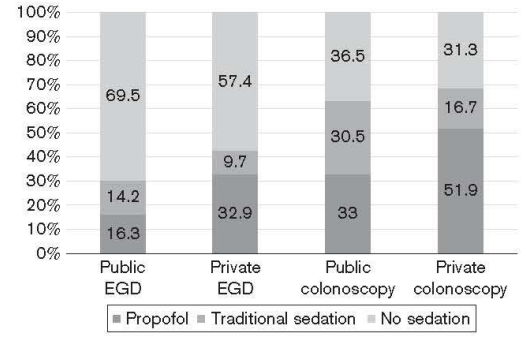
There was a highly significant difference in the usage of propofol for both EGD and colonoscopy when comparing the work setting (private vs. public), with a mean difference (MD) of 27.19±14.18% ($P=0.001$) for EGD and 22.14±36.46% ($P<0.0001$) for colonoscopy, comparing data from endoscopists who worked in both settings.

Table 1 Demographic and workplace characteristics of the survey respondents

Characteristics	$N=129$
Male sex [*n* (%)]	74 (57)
Mean age (years) (mean±SD)	45±11
Residents [*n* (%)]	14 (10)
Public hospital only [*n* (%)]	21 (18)
Private practice only [*n* (%)]	28 (24)
Public and private practice [*n* (%)]	66 (57)
Number of public EGD/month [median (IQR)]	32 (20–50)
Number of public colonoscopies/month [median IQR]	40 (30–60)
Number of private EGD/month [median (IQR)]	40 (20–90)
Number of private colonoscopies/month [median (IQR)]	50 (30–100)

EGD, esophagogastroduodenoscopy; IQR, interquartile range.

Fig. 1



Sedation practices. Mean percentage of procedures performed with no sedation, traditional sedation (benzodiazepine±opioid), and propofol-based sedation for EGD and colonoscopy in public and private settings. EGD, esophagogastroduodenoscopy.

Similarly, the absence of sedation was more common in the public setting than in the private sector for EGD (MD 20.23±14.68%; $P<0.0001$) and for colonoscopy (MD 9.42±29.9%; $P=0.021$).

Participants were asked about which agents they used and the usual dose range (on the basis of the German survey, but with lower cut-offs). The most commonly used drugs were propofol (private practice) and midazolam (public hospitals), followed by butylscopolamine, pethidine, and fentanyl. The usual doses used for colonoscopy are described in Table 2. Seldom used agents included droperidol, tramadol, paracetamol, diazepam, and alprazolam.

In terms of the recovery times, respondents answered that there were no significant differences between the

Table 2 Usual doses of the most commonly used agents for sedation in colonoscopy

Drug dosage	*N* (%)
Propofol (mg)	
<50	4 (5.6)
50–200	55 (77.5)
>200	12 (16.9)
Total	71
Midazolam (mg)	
<2	8 (12.1)
2–5	50 (75.8)
>5	8 (12.1)
Total	66
Pethidine (mg)	
<25	6 (27.3)
25–50	16 (72.7)
Total	22
Fentanyl (μg)	
<25	5 (38.5)
25–50	8 (61.5)
Total	13

mean recovery times with the use of midazolam and propofol (36.7±37.3 vs. 38±30.8 min; $P=0.314$).

Endoscopist satisfaction

The satisfaction level of the endoscopist with the quality of sedation was measured using a 10-point scale and the results are presented in Fig. 2. Propofol was the preferred sedation for both EGD (MD 3.0; $P<0.00001$) and colonoscopy (MD 2.7; $P<0.00001$) compared with midazolam. Propofol was assigned 10 points by 75.8 and 76.8% for EGD and colonoscopy, respectively. Midazolam was rated 10 only once (0.9%) and only for EGD. Midazolam was slightly preferred over no sedation for EGD (MD 0.82; $P=0.013$) and colonoscopy (MD 1.95; $P<0.00001$).

The most important limitations for procedures without sedation were patient discomfort (87.9%) and poor patient collaboration (59.6%). These were also the top two limitations pointed out for traditional sedation (39.7 and 38.5%), with the rest being prolonged recovery (26.9%) and induction times (19.2%), and cardiorespiratory complications (19.2%). For propofol sedation, the concerns were prolonged recovery (13.7%), patient loss of work time (12.3%), and cardiorespiratory complications (9.6%).

Nonanesthesiologist administration of propofol

Only 3 (2.6%) gastroenterologists reported the utilization of endoscopist-directed propofol administration and 1 (0.9%) used a second physician (nonanesthesiologist) who was responsible for the sedation.

The main reasons for the absence of NAAP were identified as lack of training (62.8%), medicolegal issues (59.0%), satisfaction with traditional sedation (12.8%), and incremental cost (5.1%). Among the respondents, 6.4% considered the presence of an anesthetist mandatory for propofol sedation, 2.6% argued that national guidelines would be necessary, and 1.3% mentioned the existing payment/reimbursement policy as a negative incentive.

When asked about the possibility of NAAP, whether adequate training and experience was acquired according to the ESGE guideline, the majority (71.2%) answered that NAAP would be a viable option, whereas 18.9% were against this and 9.9% were unsure/had no opinion. There was a nonsignificant trend for increasing age to be associated with the answer 'no' [odds ratio (OR) 1.041; 95% confidence interval (CI) 995–1.090; $P=0.083$]. An interesting observation was that 11 out of the 12 residents considered NAAP as a possibility and only one was unsure. The major concerns pointed out were, once again, lack of training and doubts on the feasibility of the procedure with only one physician.

Most respondents have professionals with training in intensive/emergency medicine or anesthesia in their endoscopy teams (63.1 vs. 34.2%).

Patient monitoring and care

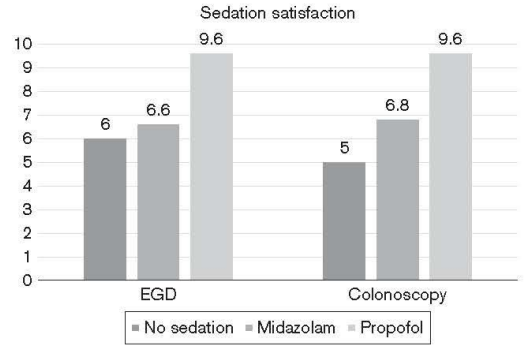
Routine oxygen supplementation is administered in 81.3% of propofol and in 41.9% with midazolam-based sedation. In terms of administration of flumazenil after a procedure with midazolam sedation, 9.9% admitted using it routinely.

Figure 3 shows the monitoring practices of the respondents.

Preferred agent

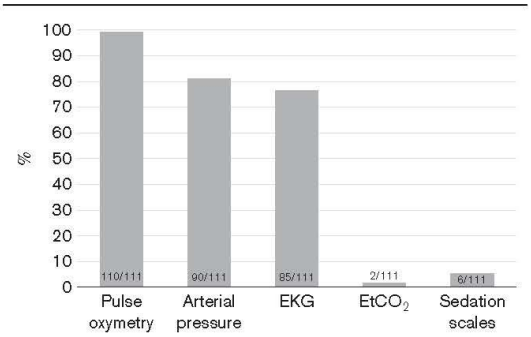
On the question of what sedation the respondents would prefer for their own colonoscopy, most mentioned propofol as the agent of choice (79.3%), followed by no sedation (16.2%) and traditional sedation (5.4%). Increasing age is associated with the option of no sedation (OR 1.052; 95% CI 1.002–1.105; $P=0.042$), but this

Fig. 2



Mean endoscopist procedural sedation satisfaction for EGD and colonoscopy with each type of sedation, assessed using a 10 (0–10) point scale. EGD, esophagogastroduodenoscopy.

Fig. 3



Monitoring practices during sedation in digestive endoscopy (traditional or propofol sedation).

effect decreases after correcting for sex (age OR 1.032; 95% CI 982–1.085; $P=0.211$; male sex hazard ratio 3.868; 95% CI 991–15.094; $P=0.52$).

When questioned on the preferred sedation for all routine colonoscopies, in a setting without logistic or financial constraints, 93.7% chose propofol, 3.6% chose traditional sedation, and 2.7% chose no sedation at all.

The main reasons pointed out as the advantages for propofol were better sedation/patient comfort (95.5%), higher quality of colonoscopy (60.4%), and shorter recovery (49.5%).

As widespread propofol sedation may not be feasible at present, question 29 inquired about the best criteria to prescribe propofol sedation. A previously failed colonoscopy was the first criterion (63.1%). Other accepted criteria were patients with an expectedly high colonoscopy burden [e.g. inflammatory bowel disease or patients at high risk for colorectal cancer (CRC)] (41.4%) or if the patient would be willing to pay the incremental cost (22.5%). A total of 53.2% of the respondents considered that propofol sedation should be accessible and proposed as an option to all patients.

Perceived impact of propofol sedation on patient compliance for endoscopic screening

A total of 82% recognized that widespread use of propofol sedation may have a positive impact on patients' acceptance and adherence to endoscopic screening for CRC, whereas 9% did not believe on such an impact. The remaining 9% were unsure of the effect.

Finally, 88.7% of the respondents believed that certified training would be useful, namely, in the gastroenterology residency program, whereas 3.8% did not see a benefit and 7.5% were unsure.

Discussion

Here, we present the results of the first Portuguese national survey focusing on the sedation aspects of digestive endoscopy. There was a 26% response rate, which is similar to the USA (27%) and German surveys (17%) [4,6], but lower than the Swiss (78%) [3], Italian (41%) [5], and Greek (40%) [1] surveys.

Portuguese endoscopists perform a median of 32–40 (public–private) EGDs and 40–50 colonoscopies/month. Those who work both in the public and in the private sector perform 60 EGDs and 85 colonoscopies/month, which is similar to the workload of American endoscopists (12.3 EGDs and 22.3 colonoscopies/week) [6] and higher than the workload of Greek endoscopists (48 EGDs and 35 colonoscopies/month) [1].

In Portugal, most EGDs are performed without sedation and most colonoscopies are performed with sedation (64% in public hospitals and 69% in the private sector), either traditional or propofol based. This figures are lower than those in the US, Germany, Canada, and Switzerland [3,4,6,17].

In the private sector, there is a higher usage of sedation for EGDs (27 vs. 47%; $P<0.001$), but only a slight increase for colonoscopy (57 vs. 68%; $P=0.021$). There was a clear preference for propofol in the private sector (33 vs. 55%; $P<0.0001$). We believe that these results can be explained by the current reimbursement protocols that may work as an incentive to use sedation in private practice, but not in public hospitals, where anesthesia professionals are preferably allocated to other tasks.

As expected, the most commonly used drugs were propofol and midazolam, with usual doses under 200 and 5 mg, respectively. The most used analgesics were pethidine and fentanyl; similar to other European countries, but unlike the USA, pethidine is favored over fentanyl [1,5]. Of note is the utilization of tramadol, paracetamol, diazepam, and alprazolam by some endoscopists, agents that have long been superseded by more effective agents for procedural sedation.

Endoscopists were satisfied with their sedation options for both EGDs and colonoscopy. No sedation was a limitation especially for colonoscopy, with a mean score of 5 out of 10. Propofol was clearly the preferred sedative, with mean scores of 9.6 for both EGD and colonoscopy. This preference was also reflected in the choice for their own sedation and is consistent with data from other national surveys [1,6]. This preference may be the result of higher ease or procedural quality, but it may also be because propofol is being administered almost always by an anesthesiologist (only four endoscopists reported using NAAP), which means that there is an extra team member in the room, decreasing the burden of patient care and possibly increasing the endoscopist comfort, even though it adds to the overall cost of the procedure.

NAAP is almost nonexistent in Portugal (3.6%), but most respondents (71.2%) would consider NAAP, given adequate formation and training. This proportion was even higher among residents (11/12; 92%) and was inversely related to age. The main obstacles to the implementation of NAAP were pointed out as being lack of training (62.8%) and medicolegal issues (59.0%). These reasons are similar to those reported in American, Greek, and Italian surveys, but the usage of NAAP is much lower in Portugal compared with 7.7% in the USA, 19% in Greece, 25% in Italy, 56% in Switzerland, and 98% in Germany.

Most (88.7%) respondents believed that certified training programs are beneficial, especially if integrated into the Gastroenterology residency curriculum. These kinds of certified training programs are mandatory in some European countries and it should be considered in Portugal as well. It is noteworthy that propofol sedation, including NAAP, has been compared with traditional sedation in several randomized-controlled trials and meta-analyses [9,18]. They have shown propofol to be as

safe as traditional sedation, while increasing patient satisfaction and allowing faster recovery and discharge times.

The preferred sedation for their own colonoscopy as well as routine colonoscopy was propofol, 79 and 94%, respectively. Older, male endoscopists seem to be more likely to prefer no sedation for themselves.

Oxygen supplementation was administered by only 81.3% with propofol and 41.9% during traditional sedation, even though it is recommended for moderate and deep levels of sedation [19,20].

Pulse oximetry and blood pressure measurements are almost universally used. EKG monitoring is used in most patients, even though it is recommended only for patients with known comorbidities. Capnography is used only by a small minority (2/111). Capnography monitoring is recommended for deep sedation by the ASA, but not by the endoscopy societies, as no clinical benefit has been shown apart from a decreased incidence of hypoxemia [21,22].

The vast majority of the respondents (81%) believed that the availability of propofol sedation for screening colonoscopy may increase population adherence to an endoscopic CRC screening program. It has been shown that sedation reduces anxiety and increases patient satisfaction and acceptance for repeat colonoscopies [23].

This survey was based on previous ones conducted in the USA and Germany, but is the first of its kind in Portugal, with the support of the Portuguese Society of Gastroenterology. It enabled us to gain insight into the current national practice of sedation in digestive endoscopy.

Still, there are some important limitations that should be acknowledged. First, only 27% of the Society members answered and thus, these results may not reflect accurately the Portuguese reality. However, there were a reasonable number of retired members or those who do not perform endoscopy. Keeping this in mind, our sample may be more representative than it appears at first glance. Second, this kind of survey has several well-known systematic biases such as recall bias and self-report bias.

In conclusion, we conducted the first Portuguese national survey on endoscopic sedation that allowed us to take a snapshot in 2014 and obtained data that may be used as a benchmarking tool (for Portugal and other countries) and help set goals and quality targets. Eventually, it may also contribute toward the elaboration of a national position statement on the subject.

Endoscopic screening is a powerful method to prevent CRC, but it is important to maximize population adherence and procedural quality, while maintaining a reasonable cost-effectiveness ratio compared with other screening strategies. NAAP may contribute toward this goal. Although endoscopists are willing to perform NAAP, the lack of training is the main cause for the lack of NAAP in Portugal. Therefore, it is reasonable to establish certified training programs for residents, fully trained specialists, and endoscopy nurses. These programs should be developed on the basis of national guidelines in concordance with the European guideline.

In the future, a second survey may allow us to gain a better understanding of the national trends in this important aspect of endoscopy.

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Conflicts of interest

There are no conflicts of interest.

References

1 Paspatis GA, Manolaraki MM, Tribonias G, Theodoropoulou A, Vardas E, Konstantinidis K, *et al.* Endoscopic sedation in Greece: results from a nationwide survey for the Hellenic Foundation of gastroenterology and nutrition. *Dig Liver Dis* 2009; **41**:807–811.

2 Liu H, Waxman DA, Main R, Mattke S. Utilization of anesthesia services during outpatient endoscopies and colonoscopies and associated spending in 2003–2009. *JAMA* 2012; **307**:1178–1184.

3 Heuss LT, Froehlich F, Beglinger C. Nonanesthesiologist-administered propofol sedation: from the exception to standard practice. Sedation and monitoring trends over 20 years. *Endoscopy* 2012; **44**:504–511.

4 Riphaus A, Geist F, Wehrmann T. Endoscopic sedation and monitoring practice in Germany: re-evaluation from the first nationwide survey 3 years after the implementation of an evidence and consent based national guideline. *Z Gastroenterol* 2013; **51**:1082–1088.

5 Fanti L, Agostoni M, Gemma M, Radaelli F, Conigliaro R, Beretta L, *et al.* Italian Society of Digestive Endoscopy Sedation Commission. Sedation and monitoring for gastrointestinal endoscopy: a nationwide web survey in Italy. *Dig Liver Dis* 2011; **43**:726–730.

6 Cohen LB, Wecsler JS, Gaetano JN, Benson AA, Miller KM, Durkalski V, Aisenberg J. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol* 2006; **101**:967–974.

7 Baudet JS, Borque P, Borja E, Alarcón-Fernández O, Sánchez-del-Río A, Campo R, Avilés J. Use of sedation in gastrointestinal endoscopy: a nationwide survey in Spain. *Eur J Gastroenterol Hepatol* 2009; **21**:882–888.

8 Bannert C, Reinhart K, Dunkler D, Trauner M, Renner F, Knoflach P, *et al.* Sedation in screening colonoscopy: impact on quality indicators and complications. *Am J Gastroenterol* 2012; **107**:1837–1848.

9 Wang D, Chen C, Chen J, Xu Y, Wang L, Zhu Z, *et al.* The use of propofol as a sedative agent in gastrointestinal endoscopy: a meta-analysis. *PLoS One* 2013; **8**:e53311.

10 Dumonceau JM, Riphaus A, Aparicio JR, Beilenhoff U, Knape JT, Ortmann M, *et al.* NAAP Task Force Members. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology Guideline: non-anesthesiologist administration of propofol for GI endoscopy. *Endoscopy* 2010; **42**:960–974.

11 American Association for the Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association Institute; American Society for Gastrointestinal Endoscopy; Society for Gastroenterology Nurses and Associates. Vargo JJ, DeLegge MH, Feld AD, Gerstenberger PD, Kwo PY, Lightdale JR, *et al.* Multisociety sedation curriculum for gastrointestinal endoscopy. *Gastroenterology* 2012; **143**: e18–e41.

12 Riphaus A, Wehrmann T, Weber B, Arnold J, Beilenhoff U, Bitter H, *et al.* Sektion Enoskopie im Auftrag der Deutschen Gesellschaft für Verdauungs- und Stoffwechselerkrankungen e.V. (DGVS); Bundesverband Niedergelassener Gastroenterologen Deuschlands e. V. (Bng); Chirurgische Arbeitsgemeinschaft für Endoskopie und Sonographie der Deutschen

Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV); Deutsche Morbus Crohn/Colitis ulcerosa Vereinigung e. V. (DCCV); Deutsche Gesellschaft für Endoskopie-Assistenzpersonal (DEGEA); Deutsche Gesellschaft für Anästhesie und Intensivmedizin (DGAI); Gesellschaft für Recht und Politik im Gesundheitswesen (GPRG). S3-guidelines – sedation in gastrointestinal endoscopy [Article in German]. *Z Gastroenterol* 2008; **46**:1298–1330.

13 Byrne MF, Chiba N, Singh H, Sadowski DC. Clinical Affairs Committee of the Canadian Association of Gastroenterology. Propofol use for sedation during endoscopy in adults: a Canadian Association of Gastroenterology position statement. *Can J Gastroenterol* 2008; **22**:457–459.

14 Schreiber F. Working Group on Endoscopy, Austrian Society of Gastroenterology and Hepatology (OGGH). Austrian Society of Gastroenterology and Hepatology (OGGH) – guidelines on sedation and monitoring during gastrointestinal endoscopy. *Endoscopy* 2007; **39**:259–262.

15 Igea F, Casellas JA, González-Huix F, Gómez-Oliva C, Baudet JS, Cacho G, *et al.* Sedation for gastrointestinal endoscopy. Clinical practice guidelines of the Sociedad Española de Endoscopia Digestiva. *Rev Esp Enferm Dig* 2014; **106**:195–211.

16 Riphaus A, Macias-Gomez C, Devière J, Dumonceau JM. Propofol, the preferred sedation for screening colonoscopy, is underused. Results of an international survey. *Dig Liver Dis* 2012; **44**:389–392.

17 Porostocky P, Chiba N, Colacino P, Sadowski D, Singh H. A survey of sedation practices for colonoscopy in Canada. *Can J Gastroenterol* 2011; **25**:255–260.

18 Singh H, Poluha W, Cheung M, Choptain N, Baron KI, Taback SP. Propofol for sedation during colonoscopy. *Cochrane Database Syst Rev* 2008; **4**: CD006268.

19 American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology* 2002; **96**:1004–1017.

20 Cohen LB, Delegge MH, Aisenberg J, Brill JV, Inadomi JM, Kochman ML, Piorkowski JD Jr. AGA Institute. AGA Institute review of endoscopic sedation. *Gastroenterology* 2007; **133**:675–701.

21 Friedrich-Rust M, Welte M, Welte C, Albert J, Meckbach Y, Herrmann E, *et al.* Capnographic monitoring of propofol-based sedation during colonoscopy. *Endoscopy* 2014; **46**:236–244.

22 Beitz A, Riphaus A, Meining A, Kronshage T, Geist C, Wagenpfeil S, *et al.* Capnographic monitoring reduces the incidence of arterial oxygen desaturation and hypoxemia during propofol sedation for colonoscopy: a randomized, controlled study (ColoCap Study). *Am J Gastroenterol* 2012; **107**:1205–1212.

23 Baudet JS, Aguirre-Jaime A. The sedation increases the acceptance of repeat colonoscopies. *Eur J Gastroenterol Hepatol* 2012; **24**:775–780.

b. NON-ANESTHESIOLOGIST ADMINISTERED PROPOFOL SEDATION FOR COLONOSCOPY IS SAFE IN LOW-RISK PATIENTS – RESULTS OF A NON-INFERIORITY RANDOMIZED CONTROLLED TRIAL

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Non-anesthesiologist administration of propofol sedation for colonoscopy is safe in low risk patients: results of a noninferiority randomized controlled trial

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Background and study aims: Propofol provides the best sedation in colonoscopy. The safety of non-anesthesiologist administration of propofol (NAAP) is still a matter of debate. The aim of the current study was to evaluate sedation safety, colonoscopy quality, and patient satisfaction with NAAP.

Patients and methods: The study was a single-blinded, noninferiority, randomized controlled trial comparing NAAP (Group A) with anesthesiologist-administered sedation (Group B) performed at a single academic institution. Patients (18–80 years) who underwent colonoscopy and were at low anesthetic risk (American Society of Anesthesiologists class I–II) were included. The primary end point was the incidence of adverse events. Secondary end points were propofol dose, patient satisfaction and pain, colonoscopy quality indicators, and procedure and recovery times.

Results: A total of 277 patients were included in the analysis. The incidence of adverse events was 39.3% in Group A and 39.0% in Group B (absolute difference −0.3%, 95% confidence interval [CI] −12.0% to 11.4%; $P=0.959$). There were no sentinel adverse events. The following interventions (Group A vs. Group B) were necessary: atropine administration (0% vs. 5.5%; $P=0.004$); airway repositioning (8.7% vs. 4.7%; $P=0.196$); increased oxygen administration (6.7% vs. 3.9%; $P=0.317$), and increased fluid rate (2.7% vs. 0.8%; $P=0.379$). There were no differences in cecal intubation and adenoma detection rates. Recovery times were longer in Group B (58±33 vs. 67±29 minutes; $P=0.032$). There were no differences in mean propofol dose, withdrawal time, painless colonoscopy, satisfaction, and amnesia. All but two patients (Group B) were willing to repeat the colonoscopy.

Conclusions: NAAP is equivalent to anesthesiologist-administered sedation in the rate of adverse events in a low risk population.

Trial registration: ClinicalTrials.gov (NCT02067065).

Introduction

Colorectal cancer (CRC) is a leading cause of cancer worldwide and is accountable for over 600 000 deaths annually [1]. Colonoscopy is the gold standard for CRC screening [2, 3]. Because colonoscopy can be an uncomfortable procedure, the use of sedation has become common in order to improve patient acceptance. Most procedures worldwide are performed using a combination of benzodiazepines and opioids to provide "conscious sedation." In the past decade, there has been a growing interest in the use of propofol for colonoscopy [4–6]. Propofol has been shown to have better pharmacokinetic and pharmacodynamic profiles than benzodiazepines [7–10], and it can achieve better patient and endoscopist satisfaction, better sedation, quicker onset, shorter recovery time, and improved colonoscopy quality [11]. Observational data suggest that these benefits may also be achieved when propofol is administered by non-anesthesiologists, without compromising patient safety [12–15].

Several guidelines have been published regarding non-anesthesiologist administration of propofol (NAAP) [16–19]. However, despite the evidence to support propofol administration by non-anesthesiologists, there are many barriers to its implementation and it is still not used in most countries [20–24]. Only one small underpowered randomized controlled trial (RCT) has compared NAAP with anesthesiologist-administered sedation. The trial suggested superiority of NAAP for colonoscopy [25], in terms of both safety and patient satisfaction.

We performed a noninferiority pilot study to compare the safety of NAAP with that of anesthesiologist-administered sedation in low risk pa-

tients undergoing routine colonoscopy in Portugal, a country where NAAP is not common [26].

Patients and methods

Patients and setting

Between January 2014 and February 2015, outpatients aged 18–80 years who were referred for elective colonoscopy were considered for inclusion in the study.

All patients were evaluated by an anesthesiologist. Exclusion criteria included American Society of Anesthesiology (ASA) class>II, pregnancy, active intravenous drug use, or patients with a predicted difficult airway and ventilation according to the anesthesiologist assessment. A "difficult airway" was defined as more than two of the following: body mass index (BMI) ≥30 kg/m^2; Mallampati score >2; neck mobility <21°; thyromental distance <6 cm; history of difficult airway or altered anatomy. "Difficult ventilation" was defined as more than two of the following: age >55 years; BMI >30 kg/m^2; presence of facial hair; history of snoring; history of obstructive sleep apnea syndrome; and mouth opening <3.8 cm.

The study was conducted at a single academic medical center. The institutional review board of Hospital Beatriz Ângelo approved the study protocol. Written informed consent for the study was obtained from all participating patients, together with informed consent for the colonoscopy. The study was also approved by the Portuguese National Data Protection Commission (CNPD). The study was registered at ClinicalTrials.gov (NCT02067065).

Study design

The study was a single-center, noninferiority RCT with two parallel intervention groups: Group A – NAAP; Group B – anesthesiologist-administered propofol-based sedation.

Intervention and team description

In Group A, sedation was performed with propofol monosedation (given as 20–40 mg boluses) by a team consisting of one endoscopist (A.O.F.) and two nurses, one of whom was exclusively dedicated to sedation and patient monitoring, according to guidelines issued by the European Society of Gastrointestinal Endoscopy (ESGE) [5]. The endoscopist had experience in intensive and emergency medicine. A total of three nurses were involved in NAAP within the study. All of the nurses had been involved in hundreds of procedures performed under anesthesia, and each nurse had performed 30 procedures of NAAP under anesthesiologist supervision as training for the study. In addition, all three nurses had advanced cardiac life support certification and had attended a theoretical NAAP course directed by A.O.F., as there is currently no certified training in Portugal.

In Group B, sedation was propofol based (also given as boluses), with other agents used at the discretion of the anesthesiologist. The team included an anesthesiologist and a dedicated sedation nurse, as well as the endoscopist and the endoscopy nurse. Nine endoscopists participated in Group B procedures in the study.

All endoscopy suites were equipped with advanced airway equipment and an anesthesia workstation (Fabius Tiro; Dräger, Wien, Austria). One cardioverter/defibrillator (HeartStart MRx, Philips, Eindhoven, The Netherlands) was available for the 3-room Endoscopy Unit.

All colonoscopies were performed using Olympus Evis-Exera II equipment (Olympus, Tokyo, Japan), with room air insufflation. Patients from both groups were administered supplemental oxygen (3 L per minute). Patients were systematically monitored by clinical observation and noninvasive arterial blood pressure measurements every 5 minutes, and continuous pulse oximetry, capnography, and electrocardiographic monitoring. Events were recorded by the assistant nurse during the endoscopic procedure. All parameters were automatically recorded at 5-minute intervals onto the patient electronic file (Innovian Anesthesia; Dräger), which was used to double check recorded events.

After the procedure, patients were evaluated every 15 minutes for discharge eligibility, according to the Chung Post-Anesthetic Discharge Scoring System (≥9) [27].

Randomization

Simple randomization was performed using www.randomization.com, and the sequence allocation was concealed from the investigators. Patients were scheduled to an endoscopy suite with or without an anesthesiologist, according to the randomization table, by a professional who was not directly involved in the study. Only patients were kept blinded. Nurses, anesthesiologists, and endoscopists were all aware of the intervention group.

Outcomes

The primary end point was the occurrence of adverse events (minor and sentinel) as defined by the World SIVA International Sedation Task Force [28]. Minor events were oxygen saturation 75%–90% for <60 seconds, transient apnea, airway obstruction, allergic reaction, failed sedation, bradycardia or tachycardia (> 25% change from baseline), hypo- or hypertension (>25% change from baseline), and seizure. Sentinel events were prolonged (>60 seconds) oxygen desaturation or <75%, prolonged apnea (>60 seconds), cardiovascular shock, and cardiac arrest.

The secondary outcomes were colonoscopy time, withdrawal time, cecal intubation rate, adenoma detection rate, propofol dose, patient satisfaction (10 point visual analog scale), pain (5-point scale), amnesia, and willingness to repeat the colonoscopy.

Sample size calculation and statistical analysis

A sample size of 320 procedures (two groups of 160) was calculated in order to obtain 90% power and a one-sided 5% significance level to exclude a 15% difference in favor of the rate of adverse events in the anesthesiologist group. The expected incidence of adverse events was 30%, and it was based on the adverse event incidence from our preliminary experience during the nurses training (90 procedures under anesthesiologist supervision).

The mean (SDs) are shown for continuous variables with a normal distribution. These were compared using an independent *t* test. The Mann-Whitney U test was used for comparison of patient pain and satisfaction scores. Categorical variables are presented as proportions (%) and were compared using the Fisher's exact test or chi-squared test. For the estimation of the primary outcome confidence interval (CI), the simple asymptotic method was used. Linear and logistic regression were used for continuous and dichotomous outcomes, respectively. Odds ratio (OR) and 95%CIs are presented. Missing data were dealt with by pairwise deletion.

The multivariable models were exploratory analyses performed to investigate the observed differences in recovery time and in patient amnesia. These statistical analyses were not on the trial protocol. We hypothesized that the utilization of other sedatives

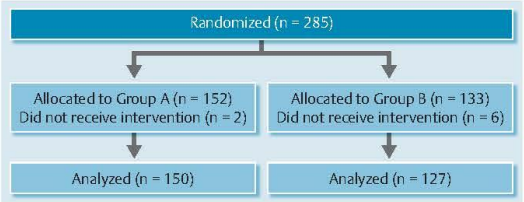

Fig. 1 Patient flow through the study.

would contribute to longer recovery and higher rates of amnesia. We built the model using only the data from Group B, as there was no use of additional sedatives in Group A (per protocol). Adjustment was made for propofol dose.

Premature ending of the trial

After the completion of 277 procedures, there was a change in institution policy. Patients were no longer evaluated by an anesthesiologist prior to sedation, and therefore the study design was violated. At this point it was decided to stop the trial.

Results

Baseline characteristics

A total of 277 colonoscopies were included, 150 in the NAAP group (Group A) and 127 in the anesthesiologist-administered sedation group (Group B) as shown in **Fig. 1**. Reasons for patients being randomized but not receiving the allocated intervention were none attendance (n = 5) and respiratory infection (n = 3) at the time of the procedure.

Groups were comparable in terms of their baseline characteristics (**Table 1**).

Procedure and sedation

Colonoscopy times and sedation parameters are shown in **Table 2**. Mean (±SD) total colonoscopy times were 2.95 ± 1.4 minutes longer in Group A compared with Group B ($P = 0.033$). In Group B, 10 patients were administered additional sedatives (midazolam and alfentanil) (**Table 3**). Propofol doses were similar between groups but were higher in Group B after adjusting for age and colonoscopy time (β coefficient 25.21, 95%CI 8.498 to 41.920; $P = 0.003$). Recovery times were longer by 8.57 ± 3.96 minutes in Group B ($P = 0.032$). This difference was independently associated with the administration of additional sedatives (mean difference 35.986, 95%CI 17.961 to 54.010; $P < 0.001$) when adjusting for propofol dose.

Table 1 Baseline patient characteristics.

	Group A[1] (n = 150)	Group B[2] (n = 127)	*P* value
Age, mean (SD), years	58.6 (13.8)	55.4 (15.4)	0.072
Male sex, n (%)	61 (40.7)	50 (39.4)	0.826
Weight, mean (SD), kg	68.7 (11.6)	70.5 (16.3)	0.303
Height, mean (SD), cm	163.1 (8.6)	163.7 (12.0)	0.660
ASA classification, n (%)			0.180
ASA I	13 (8.7)	18 (14.2)	
ASA II	137 (91.3)	107 (84.3)	
Cardiovascular disease, n (%)	20 (13.3)	12/115 (10.4)	0.569
Smoking, n (%)	24/133 (18.0)	20/114 (17.5)	1.0
Snoring history, n (%)	17/130 (13.1)	24/110 (21.8)	0.086
Heart rate, mean (SD), bpm	72.4 (13.2)	75.0 (13.8)	0.114
Arterial pressure, mean (SD), mmHg	99.3 (14.5)	98.4 (15.1)	0.595
Indication for colonoscopy, n (%)			0.851
Screening/surveillance	78 (52.0)	64 (50.4)	
Rectal bleeding	21 (14.0)	14 (11.0)	
Abdominal pain	8 (5.3)	10 (7.9)	
Inflammatory bowel disease	10 (6.7)	13 (10.2)	
Altered bowel movements	20 (13.3)	14 (11.0)	
Polypectomy	6 (4.0)	5 (3.9)	
Other	7 (4.7)	7 (5.5)	

ASA, American Society of Anesthesiologists; bpm, beat per minute.
[1] Group A = non-anesthesiologist administration of propofol.
[2] Group B = anesthesiologist-administered sedation.

Table 2 Procedure times and sedation dose.

	Group A[1] (n = 150)	Group B[2] (n = 127)	*P* value
Colonoscopy time, mean (SD), minutes	21.6 (13.0)	18.6 (9.9)	0.033
Withdrawal time, mean (SD), minutes	11.4 (9.8)	9.8 (7.5)	0.154
Propofol dose, mean (SD), mg	215 (92)	230 (97)	0.205
Additional sedatives, n (%)	0 (0)	10 (7.9)	N/A
Recovery time, mean (SD), minutes	58 (33)	67 (29)	0.032

N/A, not applicable as per protocol.
[1] Group A = non-anesthesiologist administration of propofol.
[2] Group B = anesthesiologist-administered sedation.

Table 3 Characteristics of patients who were administered additional sedatives.

	Sex	Age, years	Propofol dose, mg	Additional sedative, name (dose in mg)	Recovery time, minutes	Adverse events
1	Female	43	120	Midazolam (1.0)	70	No
2	Female	69	90	Midazolam (1.0)	60	No
3	Female	55	130	Midazolam (2.0)	65	No
4	Female	48	200	Midazolam (3.0)	60	No
5	Female	69	350	Midazolam (3.0)	240	Hypertension, vomiting
6	Female	44	270	Alfentanil (0.5)	N/D	Bradycardia
7	Male	41	290	Alfentanil (0.3)	135	Hypertension
8	Female	59	320	Alfentanil (0.5)	90	No
9	Female	27	350	Midazolm (2.0)	N/D	No
10	Male	21	480	Midazolam (3.0)	75	No

N/D, not determined.

Table 4 Incidence of adverse events.

	Group A[1] (n = 150)	Group B[2] (n = 127)	*P* value
Hypotension, n (%)	27 (18.0)	16 (12.6)	0.216
Bradycardia, n (%)	26 (17.3)	26 (20.5)	0.505
Hypoxemia, n (%)	14 (9.3)	8 (6.3)	0.352
Tachycardia, n (%)	2 (1.3)	6 (4.7)	0.093
Airway obstruction, n (%)	0 (0)	1 (0.8 %)	0.458
Others	0	2 (1.6)	0.209

[1] Group A = non-anesthesiologist administration of propofol.
[2] Group B = anesthesiologist-administered sedation.

Table 5 Reported interventions.

	Group A[1] (n = 150)	Group B[2] (n = 127)	*P* value
Airway repositioning, n (%)	13 (8.7)	6 (4.7)	0.196
Increased supplemental oxygen, n (%)	10 (6.7)	5 (3.9)	0.317
Atropine administration, n (%)	0 (0)	7 (5.5)	0.004
Rapid intravenous fluids, n (%)	4 (2.7)	1 (0.8)	0.379

[1] Group A = non-anesthesiologist administration of propofol.
[2] Group B = anesthesiologist-administered sedation.

Adverse events

There was no difference in the primary end point between the two groups. The incidence of adverse events was within the prespecified noninferiority margin, with 39.3% in Group A and 39.0% in Group B (absolute difference −0.3%, 95%CI −12.0% to 11.4%; *P* = 0.959). There were no sentinel events. **Table 4** shows the incidence of each adverse event by intervention group, and **Table 5** shows the interventions performed.

Atropine administration for bradycardia was more frequent in Group B (0% vs. 5.5%). Butylscopolamine was more often used in Group A (14.0% vs. 1.5%). This was because the endoscopist (A.O.F.) routinely used this drug to reduce colonic contractions and to improve mucosal visualization.

There was one case of transient airway obstruction in Group B, which was managed by airway repositioning and increased supplemental oxygen.

Patient satisfaction

Table 6 summarizes patient satisfaction and evaluation of the sedation quality. Overall, patients were satisfied with the sedation, with low pain scores and high amnesia rates. Almost all of the patients reported that they would repeat the colonoscopy with the same sedation and would recommend it to their families. There were no significant differences between the two groups.

There was a trend towards a higher amnesia rate in Group B (83.9% vs. 90.8%; *P* = 0.093). This result may be explained by the administration of other sedatives (midazolam/alfentanil), as there was a significant association (OR 5.704; 95%CI 1.186 to 27.428; *P* = 0.030) after adjusting for propofol dose and when looking specifically at the anesthesiologist-administered sedation group.

Colonoscopy quality

There was no significant difference in the main quality indicators. The adenoma detection rates were 28.4% in Group A and 23.2% in Group B (*P* = 0.331). The cecal intubation rates were 94.7% and 96.1% (*P* = 0.584), respectively, and the mean (±SD) withdrawal time was 11.4 ± 9.8 and 9.8 ± 7.5 minutes, respectively (*P* = 0.154).

Discussion

This is the largest RCT comparing the safety of NAAP with that of anesthesiologist-administered sedation. The results showed that in a low risk population, both procedures were equivalent in terms of adverse events, colonoscopy quality outcome measures, and patient satisfaction.

Colonoscopy is currently the preferred screening method for CRC but it is associated with pain and discomfort, which may lead to a low uptake. In order to make it less unpleasant, and to increase patients' acceptance and adherence, sedation is increasingly being used.

Traditional sedation (benzodiazepine with or without an opioid) is the most commonly used strategy. During the past decade propofol has been studied as an alternative. Propofol-based sedation

Table 6 Patients reported outcomes.

	Group A[1] (n = 150)	Group B[2] (n = 127)	*P* value
Pain (10 point VAS), %	n = 133	n = 99	0.319
0	111 (83.5)	88 (88.9)	
1	10 (7.5)	1 (1.0)	
2	6 (4.5)	5 (5.1)	
3	4 (3)	1 (1.0)	
4	1 (0.8)	2 (2.0)	
5	1 (0.8)	1 (1.0)	
7	0 (0)	1 (1.0)	
Satisfaction (1 – 5), %			0.590
2	1/148 (0.7)	1/111 (0.9)	
3	2/148 (1.4)	2/111 (1.8)	
4	23/148 (15.5)	14/114 (12.3)	
5	122/148 (82.4)	97/114 (85.1)	
Amnesia, %	125/149 (83.9)	109/120 (90.8)	0.093
Willingness to repeat, %	149/149 (100)	118/120 (98.3)	0.114
Would recommend, %	148/149 (99.3)	118/120 (98.3)	0.440

VAS, visual analog scale.
[1] Group A = non-anesthesiologist administration of propofol.
[2] Group B = anesthesiologist-administered sedation.

has been compared with traditional sedation in several trials and meta-analyses of RCTs [12, 13, 29, 30]. There is no evidence for an increased risk of adverse events with propofol. However, propofol sedation for digestive endoscopy is still underused in many countries [20, 22, 26, 31], and is mostly administered by anesthesiologists. In Germany, Switzerland, and a few other countries where NAAP is accepted, the usage of propofol is much higher [32, 33].

Several guidelines recommend the utilization of propofol by endoscopists as a safe and effective alternative to traditional sedation [5, 16, 18, 19, 34]. The ESGE even elaborated a training curriculum for the professionals involved in sedation [6]. These guidelines derive from the experimental evidence but also from a large body of observational data supporting the safety of propofol administration by non-anesthesiologists [8, 15, 35]. The other main obstacles to more widespread use of propofol sedation include costs and lack of anesthesiologists to staff the procedures.

The incremental cost per life – year gained by anesthesiologist sedation was calculated by Rex et al. to be US$5.3 million [8]. For the current study, we involved the Anesthesiology Department of the Hospital Beatriz Ângelo in the training of the nurses who were selected for the NAAP group. All procedures were performed with an anesthesiologist present in the Endoscopy Unit (but not in the same room). Overall, the two groups were balanced in terms of patient characteristics, as shown in **Table 1**.

In the final analysis, the groups had a very similar incidence of adverse events (39.3% and 39.0%; absolute difference –0.3%, 95%CI – 12.0% to 11.4%; $P = 0.959$), which allowed us to determine the noninferiority of NAAP. However, it is important to acknowledge the wide CIs obtained for this primary outcome.

The most significant adverse event was bradycardia requiring atropine. This intervention was exclusive to the anesthesiologist group (0 vs. 5.5%; $P = 0.004$). The intensive monitoring and detailed event reporting strategy followed in the study resulted in a higher than expected number of events being detected, albeit with no clinical consequences.

An interesting finding was the shorter recovery time in the NAAP group (mean difference 8.57 ± 3.96 minutes; $P = 0.032$). This difference may be explained by the administration of other sedatives in Group B, as there was a significant difference (mean difference 35.986, 95%CI 17.961 to 54.010; $P < 0.001$) when adjusting for propofol dose. This difference may have an impact on the productivity of the Endoscopy Unit.

There were no significant differences in the quality indicators of the colonoscopy, including the adenoma detection rate.

No significant differences were found in the rate of specific events, although the study was not powered to address this question. The only interventions that were different between groups were the administration of atropine and butylscopolamine. Atropine was not used in the NAAP group, perhaps because butylscopolamine was more commonly administered in Group A (it has a chronotropic effect).

Colonoscopy was well accepted by almost the entire study group irrespective of sedation protocol; most were satisfied and willing to repeat the procedure. This observation adds to the value of propofol-based sedation for digestive endoscopy.

Poincloux et al. performed a randomized trial comparing NAAP with anesthesiologist-administered sedation [25], with patient satisfaction as the primary end point. A total of 90 patients were randomized and the study failed to show a difference in the primary end point. A lower adverse event rate was observed in the NAAP group, which was associated with lower mean propofol dose.

There is still an ongoing debate concerning whether or not NAAP should be permitted. Most anesthesia societies have opposed NAAP [36] but lack the evidence to support their rationale of increased risk. There is increasing evidence to support the safety and feasibility of NAAP under strict conditions, alongside the favorable cost-effectiveness of NAAP and the importance of CRC screening. Therefore, it should lead to the adoption of the existing European Training Curriculum, which is based on cooperation between gastroenterologists and anesthesiologists to fulfill the preconditions of certification, which should take place on a national basis.

Limitations

The major limitation of the study design is the clinical relevance of the adverse event chosen as the primary end point. If "harder" and more relevant end points (e.g. cardiac arrest, prolonged apnea, or shock) had been chosen then a sample size of several hundred thousand patients would have been required. These rare end points can only be studied with large observational databases [8, 35]. In the current study there was no such event. There was no need for endotracheal intubation or bag mask ventilation.

The sedation protocol allowed the anesthesiologist to administer other sedatives/analgesics at his discretion. This may seem to limit our ability to compare the monitoring but it was felt beforehand that this was a more realistic approach, as we believe the issue is the comparison of propofol sedation without anesthesiologist support and sedation by an anesthesiologist.

A possible limitation to the external validity is the single endoscopist in Group A. Only A. O. F. was assigned to perform NAAP because of his experience in intensive/emergency medicine and airway management. Despite this limitation, we believe that as there was no need to perform advanced airway support, it is unlikely that the results would have been different with a less-experienced physician assigned to NAAP. However, it should be emphasized that according to the current European guidelines, the defined skills of the individual responsible for NAAP (including nurses) is an absolute precondition before considering NAAP for sedation. Although Group A had one endoscopist whereas Group B had nine, it is unlikely that this difference constitutes a significant bias as the outcomes of interest were not endoscopy related. The endoscopist, anesthesiologist, and nurses were aware of the intervention group. To minimize any bias, the primary end point was reported by the NAAP sedation nurse in Group A and by the anesthesiologist in Group B. A double check was then performed using the electronic health records (pulse, pulse oximetry, arterial pressure, and drug administration).

An issue that arose near the end of the study was the change in the institution policy regarding the need for an anesthesiology evaluation in an appointment prior to the procedure. This change was due to a decision by the Anesthesiology Department and was unrelated to the study. As the protocol specified that randomization would occur after that appointment, we were faced with an important decision. It was decided that the most sensitive option would be to halt the trial and avoid a possible selection bias. This decision was made by the investigators, not the Ethics Committee. Although we did not reach the calculated sample size, the effect estimate was within the prespecified noninferiority threshold.

Conclusion

In conclusion, in the safety analysis, NAAP was noninferior to anesthesiologist-administered sedation in a low risk (ASA I–II) population undergoing colonoscopy. Adverse events are common during sedation but can be safely managed by a trained team. Propofol provides high quality sedation by achieving high patient satisfaction scores and willingness to repeat colonoscopy rate.

Competing interests: None

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References

1 *Ferlay J, Shin H, Bray F* et al. GLOBOCAN 2008 v2.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 10. Lyon, France: International Agency for Research on Cancer; 2010: Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
2 *Qaseem A, Denberg TD, Hopkins RH Jr* et al. Screening for colorectal cancer: a guidance statement from the American College of Physicians. Ann Intern Med 2012; 156: 378–386
3 *Rex DK, Johnson DA, Anderson JC* et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009; 104: 739–750
4 *Vargo JJ, DeLegge MH, Feld AD* et al. Multisociety sedation curriculum for gastrointestinal endoscopy. Gastroenterology 2012; 143: e18–41
5 *Dumonceau JM, Riphaus A, Aparicio JR* et al. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology Guideline: Non-anesthesiologist administration of propofol for GI endoscopy. Endoscopy 2010; 42: 960–974
6 *Dumonceau JM, Riphaus A, Beilenhoff U* et al. European curriculum for sedation training in gastrointestinal endoscopy: position statement of the European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA). Endoscopy 2013; 45: 496–504
7 *Lichtenstein DR, Jagannath S, Baron TH* et al. Sedation and anesthesia in GI endoscopy. Gastrointest Endosc 2008; 68: 205–216
8 *Rex DK, Deenadayalu VP, Eid E* et al. Endoscopist-directed administration of propofol: a worldwide safety experience. Gastroenterology 2009; 137: 1229–1237
9 *Kazama T, Takeuchi K, Ikeda K* et al. Optimal propofol plasma concentration during upper gastrointestinal endoscopy in young, middle-aged, and elderly patients. Anesthesiology 2000; 93: 662–669
10 *Vargo JJ, Zuccaro G Jr, Dumot JA* et al. Gastroenterologist-administered propofol versus meperidine and midazolam for advanced upper endoscopy: a prospective, randomized trial. Gastroenterology 2002; 123: 8–16
11 *Bannert C, Reinhart K, Dunkler D* et al. Sedation in screening colonoscopy: impact on quality indicators and complications. Am J Gastroenterol 2012; 107: 1837–1848
12 *Wang D, Chen C, Chen J* et al. The use of propofol as a sedative agent in gastrointestinal endoscopy: a meta-analysis. PLoS One 2013; 8: e53311
13 *McQuaid KR, Laine L.* A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. Gastrointest Endosc 2008; 67: 910–923
14 *Singh H, Poluha W, Cheung M* et al. Propofol for sedation during colonoscopy. Cochrane Database Syst Rev 2008: DOI 10.1002/14651858 CD006268.pub2: CD006268
15 *de Paulo GA, Martins FPB, Macedo EP* et al. Sedation in gastrointestinal endoscopy: a prospective study comparing nonanesthesiologist-administered propofol and monitored anesthesia care. Endosc Int Open 2015; 03: E7–E13
16 *Igea F, Casellas JA, Gonzalez-Huix F* et al. Sedation for gastrointestinal endoscopy. Clinical practice guidelines of the Sociedad Espanola de Endoscopia Digestiva. Rev Esp Enferm Dig 2014; 106: 195–211
17 *Dumonceau JM, Riphaus A, Aparicio JR* et al. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology Guideline: Non-anaesthesiologist administration of propofol for GI endoscopy. Eur J Anaesthesiol 2010; 27: 1016–1030
18 *Riphaus A, Wehrmann T, Weber B* et al. [S3-guidelines–sedation in gastrointestinal endoscopy]. Z Gastroenterol 2008; 46: 1298–1330
19 *Vargo JJ, Cohen LB, Rex DK* et al. Position statement: Nonanesthesiologist administration of propofol for GI endoscopy. Gastroenterology 2009; 137: 2161–2167
20 *Riphaus A, Macias-Gomez C, Deviere J* et al. Propofol, the preferred sedation for screening colonoscopy, is underused. Results of an international survey. Dig Liver Dis 2012; 44: 389–392
21 *Faulx AL, Vela S, Das A* et al. The changing landscape of practice patterns regarding unsedated endoscopy and propofol use: a national Web survey. Gastrointest Endosc 2005; 62: 9–15

22 *Cohen LB, Wecsler JS, Gaetano JN* et al. Endoscopic sedation in the United States: results from a nationwide survey. Am J Gastroenterol 2006; 101: 967 – 974
23 *Paspatis GA, Manolaraki MM, Tribonias G* et al. Endoscopic sedation in Greece: results from a nationwide survey for the Hellenic Foundation of gastroenterology and nutrition. Dig Liver Dis 2009; 41: 807 – 811
24 *Riphaus A, Rabofski M, Wehrmann T.* Endoscopic sedation and monitoring practice in Germany: results from the first nationwide survey. Z Gastroenterol 2010; 48: 392 – 397
25 *Poincloux L, Laquiere A, Bazin JE* et al. A randomized controlled trial of endoscopist vs. anaesthetist-administered sedation for colonoscopy. Dig Liver Dis 2011; 43: 553 – 558
26 *Ferreira AO, Torres J, Dinis-Ribeiro M* et al. Endoscopic sedation and monitoring practices in Portugal: a nationwide web-based survey. Eur J Gastroenterol Hepatol 2015; 27: 265 – 270
27 *Chung F, Chan VW, Ong D.* A post-anesthetic discharge scoring system for home readiness after ambulatory surgery. J Clin Anesth 1995; 7: 500 – 506
28 *Mason KP, Green SM, Piacevoli Q.* Adverse event reporting tool to standardize the reporting and tracking of adverse events during procedural sedation: a consensus document from the World SIVA International Sedation Task Force. Br J Anaesth 2012; 108: 13 – 20
29 *Wang D, Wang S, Chen J* et al. Propofol combined with traditional sedative agents versus propofol- alone sedation for gastrointestinal endoscopy: a meta-analysis. Scand J Gastroenterol 2013; 48: 101 – 110
30 *Qadeer MA, Vargo JJ, Khandwala F* et al. Propofol versus traditional sedative agents for gastrointestinal endoscopy: a meta-analysis. Clin Gastroenterol Hepatol 2005; 3: 1049 – 1056
31 *Lucendo AJ, Gonzalez-Huix F, Tenias JM* et al. Gastrointestinal endoscopy sedation and monitoring practices in Spain: a nationwide survey in the year 2014. Endoscopy 2015; 47: 383 – 390
32 *Riphaus A, Geist F, Wehrmann T.* Endoscopic sedation and monitoring practice in Germany: re-evaluation from the first nationwide survey 3 years after the implementation of an evidence and consent based national guideline. Z Gastroenterol 2013; 51: 1082 – 1088
33 *Heuss LT, Froehlich F, Beglinger C.* Nonanesthesiologist-administered propofol sedation: from the exception to standard practice. Sedation and monitoring trends over 20 years. Endoscopy 2012; 44: 504 – 511
34 *Schreiber F.* Austrian Society of Gastroenterology and Hepatology (OGGH) – guidelines on sedation and monitoring during gastrointestinal endoscopy. Endoscopy 2007; 39: 259 – 262
35 *Sieg A, Beck S, Scholl SG* et al. Safety analysis of endoscopist-directed propofol sedation: a prospective, national multicenter study of 24 441 patients in German outpatient practices. J Gastroenterol Hepatol 2014; 29: 517 – 523
36 *Perel A.* Non-anaesthesiologists should not be allowed to administer propofol for procedural sedation: a consensus statement of 21 European national societies of anaesthesia. Eur J Anaesthesiol 2011; 28: 580 – 584

CHAPTER III.

IMPROVING THE EFFECTIVENESS OF COLONOSCOPY

a. ADENOMA DETECTION RATE: I WILL SHOW YOU MINE IF YOU SHOW ME YOURS

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Adenoma Detection Rate: I Will Show You Mine if You Show Me Yours

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Keywords

Adenoma · Colonoscopy · Colorectal neoplasms · Quality of health care · Quality health care indicators

Abstract

Background: Colorectal cancer (CRC) is the first cause of cancer-related mortality in Portugal. CRC screening reduces disease-specific mortality. Colonoscopy is currently the preferred method for screening as it may contribute to the reduction of CRC incidence. This beneficial effect is strongly associated with the adenoma detection rate (ADR). ***Aim:*** Our aim was to evaluate the quality of colonoscopy at our unit by measuring the currently accepted quality parameters and publish them as benchmarking indicators. ***Methods:*** From 5,860 colonoscopies, 654 screening procedures (with and without previous fecal occult blood testing) were analyzed. ***Results:*** The mean age of the patients was 66.4 ± 7.8 years, and the gender distribution was 1:1. The overall ADR was 36% (95% confidence interval [CI] 32–39), the mean number of adenomas per colonoscopy was 0.66 (95% CI 0.56–0.77), and the sessile serrate lesion detection rate was 1% (95% CI 0–2). The bowel preparation was rated as adequate in 496 (76%) patients. The adjusted cecal intubation rate (CIR) was 93.7% (95% CI 91.7–95.8). Most colonoscopies were performed under monitored anesthesia care (53%), and 35% were unsedated. The use of sedation (propofol or midazolam based) was associated with a higher CIR with an odds ratio of 3.60 (95% CI 2.02–6.40, $p < 0.001$). ***Conclusion:*** Our data show an above-standard ADR. The frequency of poor bowel preparation and the low sessile serrated lesion detection rate were acknowledged, and actions were implemented to improve both indicators. Quality auditing in colonoscopy should be compulsory, and while many units may do so internally, this is the first national report from a high-throughput endoscopy unit.

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Taxa de Deteção de Adenomas: Revelo a Minha Se Revelares a Tua

Palavras Chave
Adenoma · Colonoscopia · Neoplasias colorrectais · Indicadores de qualidade em assistência à saúde · Qualidade de cuidados de saúde

Resumo
O cancro do colon e reto (CCR) é a primeira causa de cancro e de morte por cancro em Portugal. O rastreio reduz a mortalidade específica por CCR. A colonoscopia é o método preferencial para o rastreio uma vez que pode contribuir para a redução da incidência do CCR. Este efeito está fortemente associado à taxa de deteção de adenomas (TDA). O nosso objetivo foi avaliar e dar a conhecer a qualidade da colonoscopia na nossa unidade, através da medição dos principais indicadores de qualidade e torná-los públicos como indicadores de aferição para outras unidades. De um total de 5,860 colonoscopias foram selecionadas para análise 654 de rastreio (com ou sem pesquisa de sangue oculto prévia). A idade média foi de 66.4 ± 7.8 anos e a distribuição por género de 1:1. A TDA global foi de 36% (95% CI 32–39), o número médio de adenomas por colonoscopia foi de 0.66 (95% CI 0.56–0.77) e a taxa de deteção de lesões serreadas sésseis foi 1% (95% CI 0–2). A preparação intestinal foi considerada adequada em 496 (76%). A taxa de intubação cecal ajustada foi de 93.7% (95% CI 91.7–95.8). A maioria das colonoscopias foi realizada sob sedação profunda/anestesia por anestesista (53%) e 35% foram sem sedação. A utilização de sedação está associada a uma maior taxa de intubação cecal (OR 3.60; 95% CI 2.02–6.40, $p < 0.001$). Estes dados revelam uma TDA superior ao mínimo definido para colonoscopia de qualidade. A frequência de preparações intestinais inadequadas e a baixa taxa de deteção de lesões serreadas sésseis são indicadores importantes que foram reconhecidos e levaram a medidas de melhoria de qualidade na nossa unidade. A auditoria de qualidade em colonoscopia deve ser realizada de forma contínua e embora muitas unidades façam auditorias internas, esta é a primeira publicação com os dados de uma unidade de endoscopia nacional.

Introduction

Colorectal cancer (CRC) is the first cause of cancer-related mortality in Portugal and a leading cause of cancer deaths in the world [1]. CRC screening reduces disease-specific mortality [2–10]. Colonoscopy is currently the preferred method for screening [11, 12] as it allows for the detection and removal of premalignant lesions and may contribute for the reduction of CRC incidence [2, 4, 5, 13, 14], which is still increasing in Portugal [1, 15]. However, this beneficial effect is strongly associated with the adenoma detection rate (ADR) [2], which is the single most important quality surrogate for screening colonoscopy [16]. Besides ADR, the European Society of Gastrointestinal Endoscopy (ESGE) published a set of indicators and the recommended quality thresholds to ensure effective screening in Europe [17].

In Portugal, there is no organized CRC screening program yet. Screening colonoscopy is performed in hospitals, ambulatory centers, or office-based endoscopy clinics, and there is no systematic audit of colonoscopy quality in place.

Health services research is increasingly being valued as a means to study the outcome of specific interventions and to establish benchmarking criteria to healthcare providers. It also enables to detect organizational underperformance in order to undertake conscientious changes.

Our aim was to evaluate the quality of colonoscopy at the Hospital Beatriz Ângelo in Loures, Portugal, in the first 3 years since its opening in 2012, having as comparators the established indicator thresholds when available.

Methods

We conducted a single-center, cross-sectional study in the secondary care hospital Hospital Beatriz Ângelo (HBA) between January 2012 and December 2014. The data were retrospectively collected.

Patients

We selected all patients ≥50 years of age who were referred to HBA directly for colonoscopy screening or following a positive fecal occult blood test (FOBT). Patients referred for colonoscopy for other indications, including surveillance after resection of colorectal lesions and a family history of CRC or adenomas, were excluded from the analysis.

All patients were pre-evaluated at a gastroenterology appointment where the written informed consent for the procedure was obtained.

Bowel preparation was accomplished using verbal and written information. Patients were informed to take a 3-day low-residue diet, a low-volume (2 L) polyethylene glycol bowel preparation

(Moviprep®; Norgine Limited, Hengoed, UK), and 2 tablets of bisacodyl 5 mg in the evening prior to the procedure for morning patients and a split-dose regimen for those in the afternoon schedule.

Setting

The Endoscopy Unit at HBA is integrated in a surgical ambulatory care center and comprises 3 endoscopy rooms equipped with Olympus Evis-Exera II (Olympus, Tokyo, Japan) video processors and endoscopes of the 160 and 180 series. The electrosurgical units are VIO 200D and 200S models (Erbe Elektromedizin GmbH, Tübingen, Germany). All rooms are equipped with an anesthesia workstation (Fabius Tiro; Drager, Vienna, Austria).

The recovery room has a total capacity of 26 patients, 10 of which are attributed to the Endoscopy Unit.

During the study period, the unit was staffed by 8 gastroenterology consultants and 1 gastroenterology resident.

Each room is staffed by an endoscopist, a nurse, and a staff assistant. For the cases performed under propofol sedation – monitored anesthesia care (MAC) – an anesthesiologist and a second nurse were also staffing the room.

Outcomes

We used the institution's electronic health record to collect individual patient demographic characteristics as well as colonoscopy quality indicators, which were as follows: ADR (calculated as the number of colonoscopies with histologically confirmed adenomas over the total number of colonoscopies); the mean number of histologically confirmed adenomas per colonoscopy; lesion detection rate (number of colonoscopies with endoscopically detected lesions over the total number of colonoscopies); number of endoscopic detected lesions per colonoscopy; advanced ADR (lesion size ≥10 mm, high-grade dysplasia, or villous histology); CRC detection rate; lesion attack rate (number of lesions removed over number of lesions detected); cecal intubation rate (CIR), crude and adjusted for stenosis); rate of cecal intubation photographic documentation; bowel preparation quality as rated by the endoscopist as adequate (good and fair) or inadequate; type of sedation (propofol based, midazolam based, or none); written surveillance recommendation rate, and complication rate (clinically significant bleeding and perforation or post-polypectomy syndrome) that involved admittance of the patient or a subsequent emergency room episode.

As quality thresholds for CIR, we used the bowel preparation quality and informed consent rate for those set by the ESGE [17], and for the remainders, we used the thresholds set by the American Society for Gastrointestinal Endoscopy (ASGE) [16].

Statistical Analysis

The mean and standard deviations are shown for continuous variables with a normal distribution. These were compared using an independent *t* test. The other continuous variables were compared using the Mann-Whitney U test.

Categorical variables are presented as proportions (%) and compared with the Fisher or χ^2 tests. For the estimation of the confidence intervals (CIs), the simple asymptotic method was used. Logistic regression was used for dichotomous outcomes in order to determine the effect estimates that are presented as odds ratio (OR) and 95% CIs. Missing data were dealt by pairwise deletion.

Table 1. Demographic and procedural characteristics

	Screening (n = 110)	FOBT (n = 544)	Total (n = 654)
Mean age ± SD, years	63.4±7.5	67.0±7.74	66.4±7.8
Male sex	57 (52)	271 (50)	328 (50)
Obesity	25 (23)	164 (30)	189 (29)
Diabetes	21 (19)	115 (21)	136 (21)
CRC family history	27 (25)	59 (11)	86 (13)
Sedation			
Propofol based	63 (57)	283 (52)	346 (53)
Midazolam based	11 (10)	66 (12)	77 (12)
No sedation	36 (33)	195 (36)	231 (35)

Values are n (%), unless otherwise indicated.

FOBT, fecal occult blood test; CRC, colorectal cancer; SD, standard deviation.

Results

From a total of 5,860 colonoscopies performed during the study period, 736 were included for review. After individual review of each patient's electronic health record, 82 were excluded as they were considered to be diagnostic procedures for symptomatic patients. The final sample was composed of 654 colonoscopies, and the demographic and procedural characteristics are depicted in Table 1.

The mean age was 66.4 ± 7.8 years, and the gender ratio was 1:1. Colonoscopy quality indicators are shown in Table 2. The overall ADR is 36% (95% CI 32–39) 45.8 and 25.1% for the male and female patients, respectively. The mean adenoma number per colonoscopy was 0.66 (95% CI 0.56–0.77).

The bowel preparation was rated by the endoscopist as adequate (excellent, good, or fair) in 496 (76%) patients. 236 (35%) patients were submitted to unsedated colonoscopy, while the majority (53%) were offered propofol-based deep sedation under anesthesiologist care.

The crude CIR was 92% (95% CI 89–94) and 93.7% (95% CI 91.7–95.8) after adjusting for stenosis and poor bowel preparation. Table 3 shows the adjusted CIR according to the sedation type. The use of sedation (propofol or midazolam based) was associated with a higher CIR with an OR of 3.60 (95% CI 2.02–6.40, $p < 0.001$). Concerning CIR, there was no statistically significant difference between propofol- or midazolam-based sedation (OR 0.88, 95% CI 0.29–2.72, $p = 0.831$).

To increase the CIR by 1, the number that needs to be sedated is 18.9.

Table 2. Colonoscopy quality indicators

	Screening (n = 110)	FOBT (n = 544)	Total (n = 654)	ASGE thresholds, %
ADR	34 (25–43)	36 (32–40)	36 (32–39)	≥25
MAPC	0.53 (0.36–0.69)	0.69 (0.57–0.81)	0.66 (0.56–0.77)	n.a.
AADR	14 (7–20)	20 (17–24)	19 (16–22)	n.a.
SSL	–	1 (0–2)	1 (0–2)	n.a.
LDR	51 (41–60)	54 (50–58)	54 (50–57)	n.a.
MLPC	0.95 (0.67–1.22)	1.09 (0.93–1.26)	1.07 (0.92–1.21)	n.a.
CRC DR	1 (0–3)	3 (1–4)	2 (1–4)	
CIR	94.4 (89.5–99.3)	93.6 (91.3–95.9)	93.7 (91.7–95.8)	≥90*
Cecal intubation documentation	94 (89–99)	91 (89–94)	92 (89–94)	≥95
Adequate bowel preparation, n (%)	81 (74)	416 (76)	496 (76)	≥85
Adverse event rate	2 (0–4)	2 (1–3)	2 (1–3)	n.a.
Surveillance recommendation	38 (29–48)	60 (55–64)	56 (52–60)	≥90

Values are 95% CI, unless otherwise indicated. FOBT, fecal occult blood test; ASGE, American Society for Gastrointestinal Endoscopy; ADR, adenoma detection rate; MAPC, mean adenoma per colonoscopy; AADR, advanced adenoma detection rate; SSL, sessile serrated lesion; LDR, lesion detection rate; MLPC, mean lesion per colonoscopy; CRC DR, colorectal cancer detection rate; CIR, cecal intubation rate; n.a., not available.

* ≥95 for screening procedures (not FOBT).

Table 3. Adjusted cecal intubation rate (CIR) by sedation type

	Propofol	Traditional sedation	No sedation
CIR, n (%)	277 (95.8)	65 (94.2)	166 (90.2)

With these data, we can calculate a number needed to diagnose of 2.8 for colorectal adenomas and 50 colonoscopies for CRC. In the subgroup of positive FOBT, the numbers were 2.8 and 33, respectively.

To calculate the cost-effectiveness ratio for CRC and adenoma detection, we used the value payed by the national health system to private units, which is set at EUR 101.23 for a colonoscopy. Accordingly, the cost for the detection and removal of an adenoma is EUR 283.44, and EUR 5,061.50 for 1 diagnosis of CRC.

Discussion

HBA is a newly built hospital (2012), and its management places an important focus on quality improvement and innovation. The current study results from this need and aims at promoting the design and implementation of specific measures to improve the outcomes.

The single most important outcome to measure the effectiveness of colonoscopy is the ADR, since it is associated with the future risk of CRC incidence and mortality [2]. The ADR at our unit (36%, 95% CI 32–39) is well above the quality threshold set by the endoscopy societies, which is currently 25% [16]. The benefit of knowing our own ADR may also motivate quality improvement, as has been shown in several interventional studies with the implementation of scheduled personalized ADR report cards. Endoscopists thrive when they are aware of their own quality metrics [18, 19].

It is our intention to maintain the audit in order to promote a continuous incentive to improve the yield of colonoscopy.

Nevertheless, although ADR is considered the best surrogate marker of colonoscopy quality, it is associated with several shortcomings such as allowing itself to be gamed while inducing a "one-and-done" performance by the practicing endoscopist [16]. To overcome this limitation, the mean number of adenomas per colonoscopy is an alternative indicator that is gaining acceptance as it possesses more information than the ADR [16, 20]. The mean number of histologically confirmed adenomas per colonoscopy in our cohort (0.66 [95% CI 0.56–0.77]) is well above the threshold of 0.5 lesions per colonoscopy proposed by the Indiana Group [20].

The very low sessile serrated lesion (SSL) detection has led us to discuss the issue with our pathologists, and we

are currently performing a large-scale randomized trial to evaluate a specific intervention to improve SSL detection. Participation in research protocols may constitute by itself an incentive to overperform, and this is a hypothesis that we will be evaluated in the future.

The CIR (93.7%) was also within the established quality threshold. The use of sedation seems to have been valuable in this regard as it was used in the majority of procedures and was associated with a higher CIR.

Regarding procedural sedation, our unit has a higher rate of propofol sedation than the reported in Portuguese public hospitals in a recent national survey [21]. The ESGE evidence-based guideline endorses the use of nonanesthesiology-administered propofol sedation [22], but the Portuguese National Health Administration (Direção Geral de Saúde) recommends the routine use of MAC for screening colonoscopy. Sedation has been extensively studied and mainly improves patients' comfort and acceptance with little (if any) added risk with anesthesia services [23].

The data presented herein support sedation use, either as moderate/traditional sedation or as MAC. The usage of sedation was associated with a higher CIR with a number need to treat of 18.9, and although we did not evaluate safety, we have previously studied propofol-based deep sedation during colonoscopy in a strictly controlled clinical trial, and there were no serious adverse events [24]. Still, there is ongoing and renewed discussion on the benefits of sedation since the NordICC trial exposed some evidence failing to associate a benefit in comfort, CIR, and ADR with sedation [25]. Moreover, concern over the potential for the increase in adverse events due to sedation reemerged with the analysis of over 3 million colonoscopy administrative claims in the USA (patients aged 40–64 years) by Wernli et al. [23], where 34% were performed with anesthesia services. In that study, anesthesia was associated with a significant increased risk for complications (OR 1.13 [95% CI 1.12–1.14]), albeit a low absolute risk. A safe and very cost-effective alternative to MAC is nonanesthesiologist administration of propofol as we have shown previously in a noninferiority randomized controlled trial, which enrolled 277 low-risk (American Society of Anesthesiologists [ASA] <3) patients [24]. Currently, we offer the option of moderate sedation to all our patients and MAC to selected patients.

One of the most important results obtained was the acknowledgement of a high proportion of patients with a bowel preparation quality considered inadequate. Almost a quarter of all procedures were deemed poorly prepared by the endoscopist. Poor bowel preparation has been associated with a lower CIR and ADR [26], as well as higher rates of adverse events and repeat procedures. This study allowed us to acknowledge the underperformance and to determine bowel preparation as a priority issue in our unit. An intervention to optimize it is now in place. The intervention consists of adopting split-dose and same-day regimens for morning and evening procedures and a newly designed written document with emphasis on simplicity. Split-dose for morning procedures has been shown to improve ADR and especially the quality of the preparation in the right bowel [27, 28]. Although, this scheme is advocated by major societies [29, 30], its uptake has been suboptimal due to factors such as fear of increased aspiration risk, fecal incontinence, and low patient education [31], even with the ASA guidelines advocating a 2-hour clear liquid fast for all forms of anesthesia in patients without risk factors for aspiration [32].

The aim of the intervention is to lower the inadequate preparations to a value <15% in order to comply with the quality metrics and improve our ADR while decreasing the number of repeat procedures. We have implemented an ongoing auditing strategy to measure the impact of the intervention, which will soon be reported.

Studies such as the present one show a commitment to quality that should be mandatory in all endoscopy units. We believe that the reports of critical quality indicators such as the ADR should be made public and wish to contribute by taking a first step towards transparency and benchmarking in colonoscopy in Portugal.

Moreover, the continuous audit of quality parameters and the comparison of benchmarks may contribute to implement proven interventions or hypothesize new interventions that may contribute to the increase in effectiveness (or safety) of colonoscopy. As this was an internal audit conducted by the endoscopy unit personnel, an obvious conflict of interest has to be acknowledged. The ideal option would be to have an external audit or natural language software to calculate the quality indicators autonomously.

As a limitation we must acknowledge the fact that most patients included were not "screening naïve" as 83% had a positive FOBT as the indication for colonoscopy. However, the ADR in both screening and FOBT groups was remarkably similar, and the estimated CIs were above 25% in both groups.

Another important limitation is the lack of a validated bowel preparation quality scale in our analysis. This is due to the retrospective design of the study and because only one-third of the procedures had reported values for each segment of the colon using a validated scale (the Bos-

ton Bowel Preparation Score). All reports used a subjective scale of poor/fair/good preparation determined by an endoscopist. Following this study, it became mandatory in our unit to systematically assess and include the preparation quality in the colonoscopy report.

The presented data also prompted us to implement a proven strategy to improve the bowel preparation quality and designed a multicenter randomized controlled trial to test a specific intervention to improve the SSL detection rate.

The ultimate goal of this study is to increase the public acceptance for colonoscopy by showing data to support its effectiveness and to decrease the incidence- and CRC-associated mortality in Portugal. Moreover, the Portuguese government recently issued an executive document in order to implement a CRC screening strategy in Portugal by 2017. Such a program has to bear in its core the awareness of the importance of quality colonoscopy. We urge colonoscopists to embrace quality metrics and make them public while external audit is not in place. Such transparency will hopefully contribute to make colonoscopy the most cost-effective screening strategy in Portugal.

Statement of Ethics

Written informed consent for the procedure was obtained by the patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

1 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, et al: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–E386.

2 Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, Zauber AG, et al: Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014;370:1298–1306.

3 Shaukat A, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS, Church TR: Long-term mortality after screening for colorectal cancer. N Engl J Med 2013;369:1106–1114.

4 Nishihara R, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, Inamura K, et al: Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;369:1095–1105.

5 Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, Shi W, et al: Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687–696.

6 Schoen RE, Pinsky PF, Weissfeld JL, Yokochi LA, Church T, Laiyemo AO, Bresalier R, et al: Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366:2345–2357.

7 Lieberman DA, Weiss DG: One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. N Engl J Med 2001;345:555–560.

8 Winawer SJ, Zauber AG, O'Brien MJ, Ho MN, Gottlieb L, Sternberg SS, Waye JD, et al: Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. N Engl J Med 1993;328:901–906.

9 Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, et al: Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977–1981.

10 Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, Ederer F: Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med 1993;328:1365–1371.

11 Qaseem A, Denberg TD, Hopkins RH Jr, Humphrey LL, Levine J, Sweet DE, Shekelle P: Screening for colorectal cancer: a guidance statement from the American College of Physicians. Ann Intern Med 2012;156:378–386.

12 Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM: American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009;104:739–750.

13 Edwards BK, Noone AM, Mariotto AB, Simard EP, Boscoe FP, Henley SJ, Jemal A, et al: Annual Report to the Nation on the status of cancer, 1975–2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer 2014;120:1290–1314.

14 Lieberman DA, Weiss DG, Harford WV, Ahnen DJ, Provenzale D, Sontag SJ, Schnell TG, et al: Five-year colon surveillance after screening colonoscopy. Gastroenterology 2007;133:1077–1085.

15 Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, et al: Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, International Agency for Research on Cancer, 2013. GLOBOCAN 2012 v1.0.

16 Rex DK, Schoenfeld PS, Cohen J, Pike IM, Adler DG, Fennerty MB, Lieb JG 2nd, et al: Quality indicators for colonoscopy. Gastrointest Endosc 2015;81:31–53.

17 Rembacken B, Hassan C, Riemann JF, Chilton A, Rutter M, Dumonceau JM, Omar M, et al: Quality in screening colonoscopy: position statement of the European Society of Gastrointestinal Endoscopy (ESGE). Endoscopy 2012;44:957–968.

18 Keswani RN, Yadlapati R, Gleason KM, Ciolino JD, Manka M, O'Leary KJ, Barnard C, et al: Physician report cards and implementing standards of practice are both significantly associated with improved screening colonoscopy quality. Am J Gastroenterol 2015;110:1134–1139.

19 Kahi CJ, Ballard D, Shah AS, Mears R, Johnson CS: Impact of a quarterly report card on colonoscopy quality measures. Gastrointest Endosc 2013;77:925–931.

20 Kahi CJ, Vemulapalli KC, Johnson CS, Rex DK: Improving measurement of the adenoma detection rate and adenoma per colonoscopy quality metric: the Indiana University experience. Gastrointest Endosc 2014;79:448–454.

21 Ferreira AO, Torres J, Dinis-Ribeiro M, Cravo M: Endoscopic sedation and monitoring practices in Portugal: a nationwide web-based survey. Eur J Gastroenterol Hepatol 2015;27:265–270.

22 Dumonceau JM, Riphaus A, Schreiber F, Vilmann P, Beilenhoff U, Aparicio JR, Vargo JJ, et al: Non-anesthesiologist administration of propofol for gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates Guideline – Updated June 2015. Endoscopy 2015;47: 1175–1189.
23 Wernli KJ, Brenner AT, Rutter CM, Inadomi JM: Risks associated with anesthesia services during colonoscopy. Gastroenterology 2016; 150:888–894.
24 Ferreira AO, Torres J, Barjas E, Nunes J, Gloria L, Ferreira R, Rocha M, et al: Non-anesthesiologist administration of propofol sedation for colonoscopy is safe in low risk patients: results of a noninferiority randomized controlled trial. Endoscopy 2016;48:747–753.
25 Bretthauer M, Kaminski MF, Loberg M, Zauber AG, Regula J, Kuipers EJ, Hernan MA, et al: Population-based colonoscopy screening for colorectal cancer: a randomized clinical trial. JAMA Intern Med 2016;176:894–902.
26 Sulz MC, Kroger A, Prakash M, Manser CN, Heinrich H, Misselwitz B: Meta-analysis of the effect of bowel preparation on adenoma detection: early adenomas affected stronger than advanced adenomas. PLoS One 2016; 11:e0154149.
27 Martel M, Barkun AN, Menard C, Restellini S, Kherad O, Vanasse A: Split-dose preparations are superior to day-before bowel cleansing regimens: a meta-analysis. Gastroenterology 2015;149:79–88.
28 Enestvedt BK, Tofani C, Laine LA, Tierney A, Fennerty MB: 4-Liter split-dose polyethylene glycol is superior to other bowel preparations, based on systematic review and meta-analysis. Clin Gastroenterol Hepatol 2012;10: 1225–1231.
29 Saltzman JR, Cash BD, Pasha SF, Early DS, Muthusamy VR, Khashab MA, Chathadi KV, et al: Bowel preparation before colonoscopy. Gastrointest Endosc 2015;81:781–794.
30 Hassan C, Bretthauer M, Kaminski MF, Polkowski M, Rembacken B, Saunders B, Benamouzig R, et al: Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2013;45:142–150.
31 Radaelli F, Paggi S, Repici A, Gullotti G, Cesaro P, Rotondano G, Cugia L, et al: Barriers against split-dose bowel preparation for colonoscopy. Gut 2016, Epub ahead of print.
32 Apfelbaum JL, Caplan RA, Connis RT, Epstein BS, Nickinovich DG, Warner MA: Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Anesthesiology 2011;114:495–511.

b. ENDOCUFF-ASSISTED COLONOSCOPY DOES NOT INCREASE THE SESSILE SERRATED LESION DETECTION RATE – A RANDOMIZED CONTROLLED TRIAL

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Endocuff-Assisted Colonoscopy Does Not increase the Sessile Serrated Lesion Detection Rate – A Randomized Controlled Trial

Background

Colorectal cancer (CRC) is the most common cancer and the second leading cause of cancer-related death, with 242 000 deaths/year[1]. Colonoscopy has been shown to decrease both the incidence of CRC and the related mortality by facilitating the detection and allowing the removal of adenomas[4,31-34,53] and is endorsed as the preferred option for CRC screening and adenoma surveillance[9,38,121,122]. The adenoma detection rate (ADR) is currently the main quality indicator for colonoscopy[66,68], as a higher ADR results in lower risks of CRC and mortality[35]. However, conventional colonoscopy has been shown to miss lesions in tandem studies, especially sessile serrated lesions (SSLs). [28,60,123]

Recently, a new endoscopic cap, Endocuff Vision™ (EV), was developed, and it is an improvement on a previous generation of Endocuff. This device is a soft plastic cap that is 2.5 cm in length with a cylindrical core and thin flexible projections fixed to the core that flatten colonic folds and stabilize the colonoscope tip, giving a better view of the entire colon.

Some studies have reported higher adenoma detection rates with Endocuff-assisted colonoscopy than with conventional colonoscopy[124-127]. The largest RCT involving EV (n=1172) showed not only a significantly higher ADR but also a significantly higher SSL detection rate (+1.1%, p=0.03)[127].

Nevertheless, the available data regarding the effectiveness of EV with regard to detecting SSLs are limited. There has been only one RCT involving patients with sessile serrated polyposis; evidence from RCTs is lacking. Few studies have specifically compared SSL detection rates between Endocuff-assisted colonoscopy and conventional colonoscopy, and those that have been performed have had conflicting results [127-130].

Consequently, randomized studies are needed to accurately evaluate the effect of Endocuff-assisted colonoscopy on SSL detection and the detection of serrated lesions at least 10 mm in size; therefore, the present study was performed.

Methods

Study design

We performed a 2-arm superiority RCT to compare SSL detection rates between Endocuff-assisted colonoscopy and conventional colonoscopy at Hospital Beatriz Ângelo.

The study was approved by the institutional review board at Hospital Beatriz Ângelo and was registered at clinicaltrials.gov (NCT03856957). All patients gave a written informed consent.

The present study adheres to Consort Guidelines.

Study population

Subjects fulfilling the following inclusion criteria were assessed for inclusion in the study: aged 40-79 years; undergoing outpatient elective colonoscopies for screening, surveillance or diagnosis; and ability to give written informed consent prior to study participation.

Subjects fulfilling any of the following criteria were excluded from the study: severe diverticulosis, colonic stricture, primary sclerosing cholangitis, inflammatory bowel disease, known polyposis syndromes, personal colorectal cancer history or previous colorectal surgery, pregnancy or breastfeeding.

Outcomes

The primary endpoint was the average number of serrated lesions ≥ 10 mm in size detected per colonoscopy in the Endocuff-assisted and conventional colonoscopy groups. This endpoint included all sessile serrated lesions and hyperplastic lesions ≥ 10 mm.

The secondary endpoints were the SSL detection rate (number of patients with at least one SSL/total number of participants); adenoma detection rate (number of patients with at least one adenoma/total number of participants); number of adenomas detected per colonoscopy (number of adenomas/total number of participants); polyp detection rate (number of patients with at least one polyp/total number of participants); number of polyps detected per colonoscopy (number of polyps/total number of participants); adenocarcinoma detection rate (number of malignant adenocarcinomas/total number of participants); caecal intubation rate; caecal incubation time; withdrawal time; and incidence of procedure-related adverse events.

Study procedures and data collection

We used a block randomization table generated in STATA, and the investigators were blinded to the random allocation. Randomization was concealed until patient assignment. Consenting patients were randomly assigned to the Endocuff-assisted colonoscopy group or the conventional colonoscopy group before the procedure with a computer-generated randomization table in REDCap. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Sociedade Portuguesa de Gastrenterologia[131,132]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails to track data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures to support data integration and interoperability with external sources.

The participating endoscopists were all experienced in optical colonoscopy (defined by having performed a minimum of 300 colonoscopies)[133]. The procedures were performed using a high-definition Olympus endoscope (CF-H190, CF-H180, PCF-H180AL/I or GIF-H180/H190). Colonoscopies were performed by one of ten endoscopists either without sedation, under conscious sedation or under deep sedation, as requested by the assistant physician. Antispasmodics (butylscopolamine) could be administered during the procedure if necessary.

The histologic evaluation of each lesion was performed by pathologists in our centre. The pathologists were blinded to the method used during the procedure.

Data collection

We recorded patient demographic and clinical data, including date of birth, sex, weight, height, body mass index, education level, smoking habits, personal history of polyps and polypectomy, date of previous colonoscopy and family history of CRC; colonoscopy data, such as the endoscopist performing the procedure, colonoscope type, indication for the procedure (screening, surveillance, or diagnosis), type of sedation (unsedated or conscious or deep sedation), the administration of antispasmodics (butylscopolamine), caecal intubation, intubation and withdrawal times, Boston Bowel Preparation Score (BBPS) in each colon segment (ascending, transverse and left colon) and adverse events; and for each lesion detected, the location, size, morphology (Paris Classification[134]) and histology (hyperplastic, adenoma, SSL or adenocarcinoma).

Sample Size

The prevalence of SSLs at the time of screening colonoscopy is close to 5% but ranges from 1 to 18%, with a mean of 1.62 lesions per patient[135,136]. For serrated lesions ≥ 10 mm, we based our estimate on Rex's trial[76], which reported 0.05 proximal lesions per colonoscopy. Based on an observational study, Endocuff may increase the SSL detection rate 5-fold. We decided to be conservative in our estimate. Therefore, considering the number of lesions per patient as the primary endpoint and aiming to have 80% power at a 5% significance level to detect a difference from 0.05 to 0.15 lesions/colonoscopy, we needed a total sample size of 198 colonoscopies. We accounted for a 2% crossover rate and therefore adjusted the sample size to 216 colonoscopies. Furthermore, based on data from our institution, we anticipated that more than 80% of patients would have adequate bowel preparation according to the validated Boston Bowel Preparation Scale (BBPS)[137]. To compensate for poor mucosal visualization and lower lesion detection due to poor preparation, we further adjusted the sample size to 254 patients.

Statistical Analysis

The statistical analysis was conducted with the SPSS software package, version 21 (Statistical Package for the Social Sciences, IBM Corporation, Armonk, NY, USA). Categorical variables are expressed as frequencies and percentages, while continuous variables are described as the means and standard deviations or medians and ranges. The chi-squared test and Fisher's exact test were used to explore associations between categorical variables. Differences in means for continuous variables and dichotomous variables were analysed by t-tests or Mann-Whitney U tests, as appropriate.

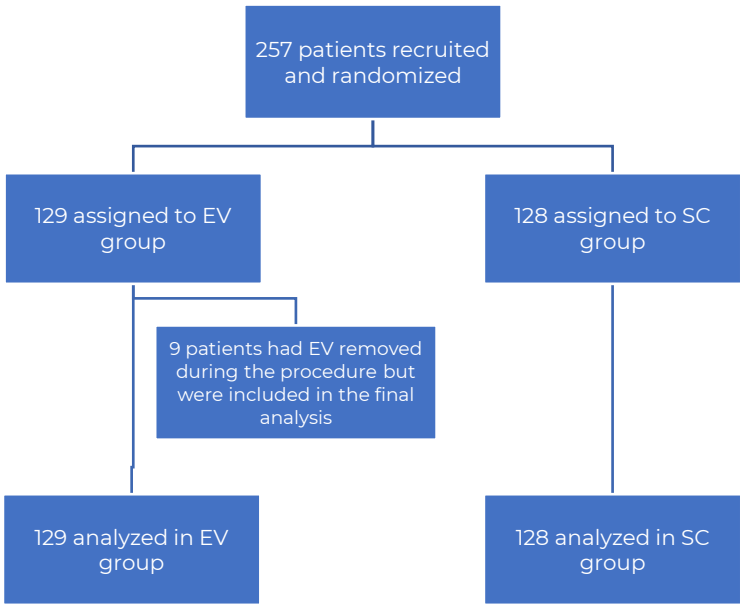
An analysis to estimate the effect of the use of Endocuff on lesion detection outcomes was conducted using logistic regression. We performed multiple regression with adjustment for withdrawal time and bowel preparation.

Results

Patient and Procedural Characteristics

A total of 257 patients were recruited and randomly assigned to the Endocuff group (n=129) and the control group (n=128). The trial profile is depicted in figure 1, and baseline characteristics were balanced, as summarized in table 1.

Figure 1. Trial profile.



SC, standard colonoscopy; EV, Endocuff Vision.

Table 1. Baseline characteristics of the study population

Characteristics	SC Group (n=128)	EV Group (n=129)	P-Value
Age, y	64.01 (9.10)	62.10 (10.04)	0.112
Male sex, n (%)	69 (53.9)	68 (52.7)	0.848
Body mass index	27.60 (3.92)	27.41 (3.81)	0.695
Family history of CRC (1st degree)	22 (17.2)	27 (20.9)	0.445
Previous colonoscopy, n (%)	59 (46.1)	59 (45.7)	0.954
Median time since last colonoscopy, months (minimum-maximum)	27 (3-144)	27 (3-230)	0.893
Personal history of polyps, n (%)	40 (31.3)	42 (32.8)	0.789
Indication • Screening • FOBT • Surveillance • Diagnostic	 19 (14.8) 12 (9.4) 38 (29.7) 59 (46.1)	 22 (17.1) 16 (12.4) 33 (25.6) 58 (45.0)	0.766

All randomized patients received the allocated intervention; however, in 9 patients, the EV was removed during the procedure, as the endoscopist found it difficult to progress to the caecum. These patients were included in the EV group as per the intention-to-treat principle. Ten endoscopists participated in the study, but 91% of the procedures were performed by six of these endoscopists; the proportions of procedures performed by these endoscopists were similar between the two groups.

The groups were also similar with regard to the procedural aspects that could impact the detection of lesions, such as bowel preparation quality and procedure durations. Procedural data are summarized in table 2.

Table 2. Procedural characteristics

Characteristics	SC Group (n=128)	EV Group (n=129)	P-Value
Deep sedation, n (%) Conscious sedation, n (%) No sedation, n (%)	15 (11.7) 103 (80.5) 10 (7.8)	17 (13.2) 98 (76.0) 14 (10.9)	0.634
Mean Boston Bowel Preparation Score			
• Left colon	2.12 (0.48)	1.99 (0.56)	0.056
• Transverse colon	2.11 (0.51)	2.04 (0.53)	0.284
• Ascending colon	2.05 (0.52)	2.02 (0.56)	0.644
• Overall	6.28 (1.41)	6.08 (1.51)	0.267
Butylscopolamine administration	11 (8.7)	12 (9.4)	0.842
Caecal intubation	124 (96.9)	123 (95.3)	0.527
Intubation time, min	7.64 (4.01)	7.03 (4.60)	0.285
Withdrawal time, min	12.82 (6.01)	11.94 (5.84)	0.259

The proportions of patients undergoing caecal intubation were similar. In 3 patients in the EV group, it was not possible to reach the caecum even after removing the device from the colonoscope due to sigmoid fixation.

Outcomes

The outcomes are summarized in table 3. There was no significant difference in the primary endpoint, that is, the number of serrated lesions ≥10 mm in size per colonoscopy, or in any of the secondary endpoints with regard to the detection of lesions, adenomas or sessile serrated lesions.

Table 3. Lesions detected stratified by study group

Characteristics	SC Group (n=128)	EV Group (n=129)	ITT OR/MD; 95% CI; p-value
PD(R), n (%)	98 (76.6)	103 (79.8)	1.213; 0.670-2.195; 0.524
ADR(R), n (%)	85 (66.4)	85 (65.9)	0.977; 0.583-1.638; 0.931
SSL detection (rate), n (%)	10 (7.8)	16 (12.4)	1.671; 0.728-3.836; 0.226
Serrated lesion ≥10 mm detection rate	3 (2.4)	8 (6.2)	2.733; 0.708-10.545; 0.145
Adenocarcinoma detection rate	2 (1.6)	2 (1.6)	0.992; 0.138-7.153; 0.994
Number of lesions, mean (SE)	2.46 (0.24)	2.91 (0.26)	0.454; -0.249-1.156; 0.204
Number of adenomas per colonoscopy	1.63 (0.22)	1.82 (0.22)	0.197; -0.421-0.814; 0.531
Number of SSLs per colonoscopy	0.156 (0.05)	0.233 (0.07)	0.0763; -0.095-0.248; 0.381
Number of serrated lesions (≥ 10 mm) per colonoscopy	0.02 (0.01)	0.06 (0.02)	0.038; -0.012-0.088; 0.131

ITT – intention to treat; OR – odds ratio; MD – mean difference; CI – confidence interval; PDR – polyp detection rate; ADR – adenoma detection rate; SSL – sessile serrated lesion.

The overall adenoma detection rate was 66.1%, the SSL detection rate was 10.1%, the rate of detection of serrated lesions ≥10 mm in size was 4.3%, and the detection rate of invasive neoplasia was 1.6%. The rate of detection of any polyp was 78.2%. The mean numbers of serrated lesions (including hyperplastic lesions ≥10 mm) were 0.233 and 0.156 (p=0.381) in the EV and control groups, respectively. The mean numbers of

adenomas were 1.821 and 1.625 (p=0.531), respectively. The differences were not significantly changed after adjusting for either BBPS or withdrawal time.

Adverse Events

There were no major adverse events in any group; however, there were 3 mucosal lacerations in the Endocuff group, while there were no mucosal lacerations in the control group. These events did not require any specific intervention.

Discussion

Our study objective was to confirm the beneficial effect of EV on the results of optical colonoscopy, specifically the detection of SSL, as they are harder to identify. We also wanted to evaluate the effect of EV on the detection of adenomas. For the primary endpoint, which was the mean number of premalignant serrated lesions, including all histologically confirmed SSLs and hyperplastic lesions ≥10 mm in size, there was a nonsignificant trend towards a higher detection rate in the EV group (MD 0.0763; 95% CI -0.095-0.248; p=0.381). There was no difference in the ADR, SSLDR, mean number of SSLs per colonoscopy or mean number of adenomas per colonoscopy.

Endocuff has been developed to improve the effectiveness of colonoscopy with regard to reducing the incidence of colorectal cancer. The first-generation Endocuff was shown to increase the adenoma detection rate[138] and decrease the adenoma miss rate[126], but not all studies showed such a clear beneficial impact, including a large RCT [128].

The largest trial of Endocuff Vision, the ADENOMA trial (n=1772), showed significant increases (4.7%, p=0.02) in the ADR and the SSL detection rate (1.1%, p=0.03), especially in the left colon, although the study was restricted to 797 patients who underwent colonoscopy for bowel cancer screening. In the non-screening colonoscopy subgroup (n=975), there was no difference between the groups.

Furthermore, SSLs are different from adenomas. They are preferentially located in the right colon, are usually flat with a mucus cap and are accompanied by subtle differences in the adjacent mucosa, which make them much harder to detect during conventional colonoscopy. Moreover, they are difficult to differentiate from hyperplastic polyps on histological examination [139], and large (≥10 mm) right colon hyperplastic polyps may in fact have invasive potential and could be managed as SSLs [22]. As a result of these characteristics, these lesions are associated with interval CRC [140,141].

In a RCT conducted in the Netherlands, the primary endpoints were the mean number of adenomas per patient and the adenoma detection rates in the Endocuff-assisted colonoscopy and conventional colonoscopy groups. The authors also evaluated the serrated lesion rate and mean number of SSLs per patient and found no differences between the two groups (27% vs. 25%, P=0.48; 0.52 ± 1.15 vs. 0.48 ± 1.05, P=0.52, respectively)[128]. However, hyperplastic polyps were also included in this analysis, and lesion size was not considered. Small purely hyperplastic lesions have a lower malignant potential; therefore, there is less interest in improving the rate of their detection than in improving that of larger serrated lesions[129]. A more recent study from the United States found a significantly higher SSL detection rate in the Endocuff-assisted colonoscopy group than in the conventional colonoscopy group (15% vs. 3%, P≤0.0001). However, that was an observational retrospective study conducted in a population of veterans, with a male predominance and multiple predisposing risks for adenomatous polyps; therefore, the results may not be generalizable to the general population[142]. In a very recent RCT on EV, which is currently the largest, higher rate of detection of both adenomas (40.9 vs 36.2%, p=0.02) and SSLs (2.3 vs 1.1%, p=0.03) were observed in the EV group[127].

Our study did not show any differences in the quality outcomes studied. While Endocuff Vision seems to be a useful add on for colonoscopy, as shown in the ADENOMA trial, its beneficial effect may be influenced by other factors, such as the skill of the endoscopist and prior detection rates.

The present study has several limitations: a relevant issue is the high overall lesion detection rate, as reflected by the ADRs of 65.9% in the EV group and 66.4% in the SC group and the SSLDRs of 12.4 and 7.8%. These are very high detection rates when compared to other trials, even if we take into account the low volume of screening procedures included (15%). In the ADENOMA trial, they had an ADR of 56% in the Bowel Screening Programme and an ADR of 24% in the non-screening colonoscopies. Although the ADRs and SSLDRs were higher than anticipated, the sample size was calculated using an estimated mean number of serrated lesions ≥10 mm in size of 0.05, which was close to what we observed, so it is

difficult to attribute the lack of difference to a lack of power in the study. Recently, a debate has started regarding whether the effectiveness of EV differs depending on the individual endoscopist. Some data suggested that “high detectors” obtained no additional benefit from using the Endocuff[143]; however, in a cluster randomized crossover trial performed in 2020, a subanalysis suggested that “high detectors” (defined as those with an ADR>25%) had a significantly higher ADR when using EV (mean difference 10.3%, p=0.001), while low detectors had a nonsignificant mean difference (6.7%, p=0.11)[144]. Our study did not allow us to explore this hypothesis due to the sample size and the fact that all endoscopists had ADRs above 40%, which may explain our results. Another limitation is that the blinding of the endoscopists was not possible to achieve, as they were always able to know whether the EV was on the scope. To overcome this limitation, we decided to perform the RCT with a single bowel exploration rather than in tandem, as this was probably the best trial design for the evaluation of a specific intervention.

Conclusion

In conclusion, our study did not show a significant difference in the detection of premalignant lesions when EV was or was not used during routine colonoscopy. There was a nonsignificant trend towards a higher rate of detection of serrated lesions in the EV group. A larger RCT in a bowel cancer screening population is needed to definitely determine the role of EV in improving the rate of detection of colonic serrated lesions.

c. NARROW BAND IMAGING VERSUS WHITE LIGHT FOR THE DETECTION OF SESSILE SERRATED COLORECTAL LESIONS: A RANDOMIZED CLINICAL TRIAL

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Cite score 1.2

Impact factor (Thomson-Reuters, 2020)

Narrow Band Imaging versus White Light for the Detection of Sessile Serrated Colorectal Lesions: a Randomized Clinical Trial

Abstract

Background: Colorectal cancer (CRC) is a leading cause of cancer. The detection of pre-malignant lesions by colonoscopy is associated with reduced CRC incidence and mortality. Narrow band imaging has shown promising but conflicting results for the detection of serrated lesions.
Methods: We performed a randomized clinical trial to compare the mean detection of serrated lesions and hyperplastic polyps ≥10 mm with NBI or high-definition white light (HD-WL) withdrawal. We also compared all sessile serrated lesions (SSL), adenoma and polyp prevalence and rates.
Results: Overall, 782 patients were randomized (WL group 392 patients; NBI group 390 patients). The average number of serrated lesions and hyperplastic polyps ≥10 mm detected per colonoscopy (primary endpoint) was similar between the HD-WL and NBI group (0.118 vs 0.156, p=0.44). Likewise, the adenoma detection rate (55.2% vs 53.2%, p=0.58) and SSL detection rate (6.8% vs 7.5%, p=0.502) were not different between the two study groups. Withdrawal time was higher in the NBI group (10.88 vs 9.47 min, p=0.004), with a statistically non-significant higher total procedure time (20.97 vs 19.30 min, p=0.052).
Conclusions: The routine utilization of narrow band imaging does not improve the detection of serrated class lesions or any pre-malignant lesion and increases the withdrawal time.

Introduction

Colorectal cancer (CRC) is a leading cause of morbidity and mortality in the world, especially in western countries [145,146]. Worldwide, CRC accounts for 860,000 deaths worldwide[146]. Colonoscopy has been shown to decrease both the incidence of CRC and the related mortality by facilitating the detection and allowing the removal of adenomas[4,31-34,53] and is endorsed as the preferred option for CRC screening and adenoma surveillance[9,38,121,122]. The adenoma detection rate (ADR) is currently the main quality indicator for colonoscopy[66,68], as a higher ADR results in lower risk of CRC and mortality[35]. However, conventional colonoscopy has been shown to miss lesions in tandem studies, especially sessile serrated lesions (SSLs). [28,60,123] These lesions are different from adenomas; they are more frequent on the right colon and usually present with a flat morphology that makes them much harder to detect through optical colonoscopy. SSL also present a different, faster carcinogenesis pathway and as result of these characteristics, they are associated with interval CRC, which is the occurrence of colorectal cancer after screening colonoscopy and before the next scheduled screening procedure [140,141].

Narrow band imaging (NBI) has been shown to be effective for SSL detection in one trial performed in an academic center and in the setting of sessile serrated polyposis [72,75]. In another RCT, Douglas Rex et al compared NBI (Olympus™ 190 series colonoscopes) and high-definition white light (HD-WL) colonoscopy for the detection of proximal serrated lesions in average risk individuals. This trial showed a trend towards higher detection in the NBI but failed to achieve statistical significance for the primary endpoint (number of proximal serrated lesions)[76]. Few other trials have studied the effect of NBI on the detection of colorectal polyps and adenomas and some have also reported the incidence of serrated class lesions with non-significant results in most of them [71,147-149]. Recently, a meta-analysis pooled the results of these trials which showed a significant increase in the detection of serrated lesions with NBI[150].

Therefore, it's still unsettled whether NBI should be used systematically during colonoscopy withdrawal to increase detection of CRC precursor lesions.

Our aim was to evaluate if the systematic usage of NBI during colonoscopywithdrawal contributes to a higher rate of SSL detection in an average CRC risk population.

Materials and Methods

Study Design

We performed a 2-arm superiority RCT to compare SSL detection between NBI and HD-WL optical colonoscopy. The study was approved by the institutional review board at Hospital Beatriz Ângelo and NOVA Medical School and was registered at clinicaltrials.gov (NCT02876133). Patients were required to sign a written informed consent.

The study was performed in one academic center between October 2016 and February 2021.

Study population

Consenting individuals fulfilling the inclusion criteria: patients scheduled for elective colonoscopies, aged 40 to 74, cecal intubation and adequate bowel preparation according to the Boston Bowel Preparation Score (BBPS) >1 in each bowel segment; and without exclusion criteria: known polyposis syndromes, primary sclerosing cholangitis, inflammatory bowel disease, personal colorectal cancer history or colorectal surgery, contraindications to polypectomy, current pregnancy and ASA >3.

Outcomes

The primary endpoint was the average number of serrated lesions including hyperplastic lesions ≥10 mm detected per colonoscopy.

The secondary endpoints were: SSL detection rate (number of patients with at least 1 SSL/total number of participants); serrated class lesions detected per colonoscopy (number of serrated lesions/total number of participants); adenoma detection rate (number of patients with at least 1 adenoma/total number of participants); adenomas detected per colonoscopy (number of adenomas/total number of participants); malignant adenocarcinoma detection rate (number of malignant adenocarcinomas/total number of participants); incidence of procedure related adverse events.

Study procedures and data collection

We used a block randomization table generated in STATA and the investigators were blinded to the random allocation. Randomization was concealed until patient assignment. Consenting patients were randomized with REDCap to the NBI group or the white light colonoscopy group, after cecal intubation and before the withdrawal. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Sociedade Portuguesa de Gastrenterologia[131,132]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails to track data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures to support data integration and interoperability with external sources.

The six participating endoscopists were all experienced in optical colonoscopy (defined by having performed a minimum of 300 colonoscopies)[133] and electronic chromoendoscopy with an ADR above 40% in all cases. The procedures were performed using a high-definition Olympus endoscope (CF-H190 or GIF-H190). Colonoscopies were performed either without sedation, under conscious sedation or under deep sedation, as requested by the assistant physician. Antispasmodics (butylscopolamine) could be administered during the procedure at the endoscopist discretion.

The histologic evaluation of each lesion was performed by pathologists in our centre. The pathologists were blinded to the method used during the procedure.

We recorded patient demographic and clinical data, including date of birth, sex, weight, height, body mass index, education level, smoking habits, personal history of polyps and polypectomy, date of previous colonoscopy and family history of CRC; colonoscopy data, such as the endoscopist performing the procedure, colonoscope model, indication for the procedure, depth of sedation (no sedation, conscious or deep sedation), the administration of antispasmodics (butylscopolamine), intubation and withdrawal times, Boston Bowel Preparation Score (BBPS) in each colon segment (ascending, transverse and left colon) and adverse events; and for each lesion detected, the location, size, morphology (Paris Classification[134]) and histology (hyperplastic, adenoma, SSL or adenocarcinoma).

Sample size

The prevalence of SSL at screening colonoscopy is close to 5% but ranges from 1 to 18%, with a mean of 1,62 lesions per case [135,136]. For serrated lesions ≥10 mm we based our estimate on Rex's trial[76] which had a proportion of 0.098 proximal lesions per colonoscopy with NBI. We believed that a 100% increase in yield could be a sufficient difference to consider routine use of NBI. Therefore, considering the number of lesions per patient as the primary endpoint and to have an 80% power at a 5% significance level to

detect a difference from 0.049 to 0.098 lesions/colonoscopy, we would need a total sample size of 968 colonoscopies. We anticipated a 2% cross-over rate and therefore we adjusted the sample size to 987 colonoscopies.

The statistical analysis was conducted with the SPSS software package, version 21 (Statistical Package for the Social Sciences, IBM Corporation, Armonk, NY, USA). Categorical variables are expressed as frequencies and percentages, while continuous variables are described as the means and standard deviations or medians and ranges. The chi-squared test and Fisher's exact test were used to explore associations between categorical variables. Differences in means for continuous variables and dichotomous variables were analysed by t-tests or Mann-Whitney U tests, as appropriate.

The study was prematurely terminated due to the significant impact of COVID19pandemic on recruitment pace.

Results

Patient and procedural characteristics

A total of 872 patients were assessed for eligibility, with 90 patients excluded before randomization due to poor bowel preparation (n=75) and failure to reach the cecum (n=15). From the included 782 patients, 390 were randomly assigned to NBI and 392 to HD-WL group. All patients received the allocated intervention. The trial profile is depicted in figure 1.

Figure 1. Trial profile.

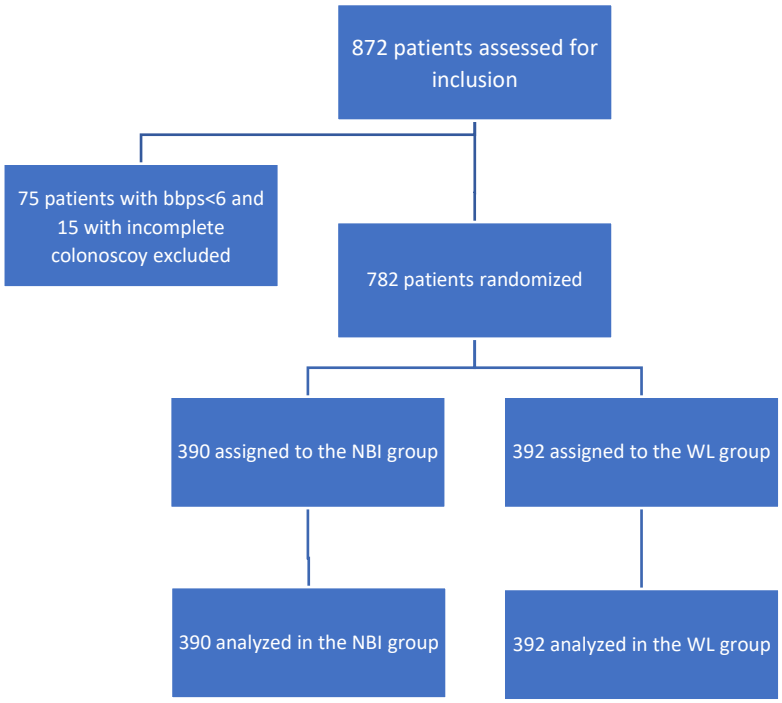

Table 1 summarizes baseline characteristics. There were no differences between the two study groups regarding age, sex, family history of CRC, personal history of polyps and colonoscopy indication.

Table 2 shows procedural characteristics. Mean withdrawal time was 1.41 minutes higher in the NBI group (10.88 vs 9.47 min, p=0.004), with a statistically non-significant higher total procedure time (20.97 vs 19.30 min, p=0.052). No significant differences were observed between the two study groups regarding depth of sedation, administration of antispasmodics (butylscopolamine) and bowel preparation quality in each colonic segment.

Table 1. Baseline characteristics of the study population

Characteristics	WL Group (n=392)	NBI Group (n=390)	P-Value
Age, y	61.44 (9.91)	60.89 (9.99)	0.444
Male sex, n (%)	204 (52.7)	212 (54.5)	0.618
Body mass index	27.67 (4.79)	27.76 (4.95)	0.813
Family history of CRC (1st degree)	93 (24.3)	68 (17.5)	0.190
Previous colonoscopy, n (%)	160 (41.5)	171 (44.0)	0.480
Median time since last colonoscopy, months (minimum-maximum)	38 (1-228)	32 (1-249)	0.081
Personal history of polyps, n (%)	111 (28.8)	119 (30.7)	0.576
Indication • Screening • FOBT • Surveillance • Diagnostic	 72 (18.8) 49 (12.8) 101 (26.3) 162 (42.2)	 89 (23.1) 61 (15.8) 103 (26.6) 133 (34.5)	 0.122

Table 2. Procedural characteristics

Characteristics	WL Group (n=392)	NBI Group (n=390)	P-Value
Deep sedation, n (%) Conscious sedation, n (%) No sedation, n (%)	130 (33.9) 209 (54.4) 45 (11.7)	135 (34.8) 221 (57.0) 32 (8.2)	 0.272
Mean Boston Bowel Preparation Score • Left colon • Transverse colon • Ascending colon	 2.26 (0.438) 2.40 (0.490) 2.45 (0.503)	 2.22 (0.415) 2.37 (0.484) 2.40 (0.495)	 0.222 0.470 0.179
Butylscopolamine administration	114 (30.2)	125 (32.7)	0.447
Total time, min	19.30 (11.32)	20.97 (10.53)	0.052
Withdrawal time, min	9.47 (6.18)	10.88 (6.37)	0.004

Outcomes

Table 3 summarizes detected lesions by study group (HD-WL vs NBI group). For the primary endpoint of the average number of serrated lesions and hyperplastic polyps ≥10 mm detected per colonoscopy, there was no significant difference between the two groups (0.118 vs 0.156, p=0.44). Overall, no differences were observed in polyp detection rate (69.6% vs 69.3%, p=0.93), adenoma detection rate (55.2% vs 53.2%, p=0.58), SSL detection rate (6.3% vs 7.5%, p=0.502) and serrated lesions including hyperplastic ≥10 mm detection rate (6.8% vs 8.9%, p=0.298) between HD-WL and NBI groups. Likewise, the number of adenomas (1.23 vs 1.23, p=0.996) and SSLs (0.11 vs 0.13, p=0.712) per colonoscopy were also not different. Finally, the adenocarcinoma detection rate also similar (1.6% vs 1.1%, p=0.535).

Table 3. Lesions detected stratified by study group

Characteristics	WL Group (n=392)	NBI Group (n=390)	ITT OR/MD; 95% CI; p-value
PD(R), n (%)	268 (69.6)	269 (69.3)	0.987; 0.727-1.340; 0.933
ADR(R), n (%)	211 (55.2)	205 (53.2)	0.923; 0.695-1.226; 0.580
SSL detection (rate), n (%)	24 (6.3)	29 (7.5)	1.212; 0.692-2.122; 0.502
Serrated lesion and hyperplastic ≥10 mm detection rate	26 (6.8)	34 (8.9)	1.326; 0.780-2.257; 0.298
Adenocarcinoma detection rate	4 (1.1)	6 (1.6)	1.496; 0.419-5.344; 0.535
Number of lesions, mean (SE)	1.92 (0.114)	2.12 (0.130)	1.034; 0.975-1.097; 0.262
Number of adenomas per colonoscopy (SE)	1.236 (0.090)	1.236 (0.112)	1.000; 0.931-1.074; 0.996
Number of SSLs per colonoscopy (SE)	0.113 (0.029)	0.130 (0.036)	1.043; 0.833-1.307; 0.712
Number of serrated lesions (≥ 10 mm) per colonoscopy (SE)	0.118 (0.029)	0.156 (0.039)	1.089; 0.876-1.355; 0.442

ITT – intention to treat; OR – odds ratio; MD – mean difference; CI – confidence interval; PDR – polyp detection rate; ADR – adenoma detection rate; SSL – sessile serrated lesion.

Discussion

We performed a randomized controlled trial design to determine whether narrow band imaging improves the detection of serrated lesions and hyperplastic lesions ≥10 mm. Our results did not show a significant difference in the detection of these lesions or in any other lesions (adenomas, sessile serrated lesions, all polyps, and invasive cancer).

Furthermore, our study was not only negative in all lesions detection outcomes, but it also showed an increased inspection (withdrawal) time by an average of 85 seconds with NBI. We believe this effect was probably associated with the known need for better washing and suction of the colon as NBI image is severely impaired by the presence of colonic residue and even clear fluids. This effect has also been seen in other trials studying NBI[150]. It is important to note the high detection rates (ADR of 54% and SSLR of 7%) in this study as the magnitude of optimization strategies decreases with high detection rates.

Strengths of this study include the randomized design and large sample size, using an endpoint that included sessile serrated lesions according to the pathologist and large hyperplastic lesions which are also a significant finding. An option would be to have all endoscopically suspicious lesions for serrated morphology double checked by a second expert digestive pathologist.

Limitations include the uncontrolled withdrawal time which was higher in the NBI group, the impossibility to blind the endoscopist, which is inevitable in these studies. However, we have previously studied and reported colonoscopy quality outcomes that may help as a benchmark. Previously we published in GE an observational study from 2012 to 2014 with a routine ADR of 36% and an SSL detection rate of 1%[137]. These figures improved in our latest report with data from 2017 to 2019 with a ADR of 55% and SSL detection rate of 4%[151]. The data shown demonstrate the overall detection improvement during routine colonoscopies in our department in recent years and is in line with the outcomes reported in our control group. Another important limitation is that our study was prematurely terminated due to COVID19 pandemic and we were 205 hundred cases short. To better understand we calculated that this sample with these results has a power of 71% to detect the prespecified effect in the sample size calculation. Therefore, it would be very unlikely that with an extension of the trial the primary endpoint would be met.

In this study we used sessile serrated lesions and large hyperplastic polyps as a combined endpoint to overcome the limitation of the known pathological identification of SSL. Unlike in Rex's trial, [152] we did not include all proximal hyperplastic lesions, and this may have contributed to a smaller effect of NBI.

This study is one of the largest randomized controlled trials studying the effect of NBI for the detection of colorectal lesions and more specifically sessile serrated lesions and large serrated class lesions. It failed to show a significant effect other than an increase in the withdrawal time.

We conclude that a beneficial detection effect of NBI is very unlikely and overwhelmed by an increase in procedural time.

d. Participation in Clinical Trials Increases the Detection of Pre-malignant Lesions during Colonoscopy

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Participation in clinical trials increases the detection of pre-malignant lesions during colonoscopy

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- Authors' Contributions

AOF was responsible for the study design, data collection and analysis and manuscript writting
MPCS collaborated in the study design analysis and manuscript critical review

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CG and BM collaborated in data collection and manuscript critical review

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ABSTRACT

Background: Colorectal adenoma detection has been associated with cancer prevention effectiveness. Clinical trials have been conceived to determine the role of several interventions to increase the detection of pre-malignant lesions. We hypothesized that colonoscopy in the setting of such trials have higher pre-malignant lesion detection rates.

Methods: We performed a cross-sectional study comparing the detection of pre-malignant lesions in 147 randomly sampled non-research colonoscopies and 294 from the control groups of two prospective trials. We included outpatients aged 40-79 who had no personal history of CRC.

Results: Baseline characteristics were similar between the two groups. The pre-malignant lesion detection rate in the trial vs control group was 65.6% vs 44.2% (OR 2.411; 95% CI 1.608-3.614; p<0.001), the polyp detection rate was 73.8% vs 59.9% (OR 1.889; 95% CI 1.242-2.876; p=0.003), the adenoma detection rate was 62.6% vs 44.2% (OR 2.110; 95% CI 1.411-3.155; p<0.001) and the sessile serrated lesion detection rate was 17% vs 4.1% (OR 4.816; 95% CI 2.014-11.515; p<0.001). The mean number of pre-malignant and sessile serrated lesions was 1.70 vs 1.06 (p=0.002) and 0.32 vs 0.06 (p=0.001) lesions per colonoscopy. In a multivariate analysis with each single potential confounder, there was no significant change in any of the study outcomes.

Conclusions: Patients involved in colonoscopy trials may benefit from higher quality examinations, as shown by the higher detection rates. Institutions should consider supporting clinical research in colonoscopy as a simple means to improve colonoscopy quality and colorectal cancer prevention.

KEY WORDS: Colonoscopy. Quality. Research. Adenoma.

INTRODUCTION

Colorectal cancer is one of the leading cancers and accounts for over 860,000 deaths worldwide.[1] Colonoscopy has been shown to decrease both CRC incidence[2] and mortality by detecting and allowing the removal of adenomas.[3-8] The magnitude of this effect is related to the detection rate of pre-malignant colorectal lesions, especially the adenoma detection rate (ADR), which is highly variable.[9-13] Sessile serrated lesions are another subset of colorectal lesions that also harbour malignant potential[14] and are harder to detect, suffering from even higher variability between endoscopists[15].

Quality in colonoscopy is therefore a major issue in digestive endoscopy, with significant efforts being made by international societies such as the European Society of Gastrointestinal Endoscopy (ESGE)[16] and the American Society of Gastrointestinal Endoscopy (ASGE)[17] to set the standards. Both societies set the adenoma detection rate as one of the most important indicators of colonoscopy quality.

In the last few decades, endoscopists and researchers have tried to improve the detection of pre-malignant lesions through technological advancements, such as high-definition imaging, electronic chromoendoscopy,[18] wide view lenses[19], devices[20,21] or artificial intelligence,[22] as well as through simple interventions such as educational sessions, feedback[23], benchmarking, changing the patient position[24], performing the colonoscopy underwater[25] or administering butylscopolamine[26] or simethicone[27]. Several of the trials of these interventions reported ADRs above 50% in some groups, including in the "placebo" arms.[18,28,29] These results are well over the proposed threshold of 25% and above our department's own indicators with an ADR of 36% and a Sessile Serrated Lesion detection of 1%,

as published in 2017.[30]

We hypothesized that patients whose colonoscopy was performed in a clinical trial setting may have higher pre-malignant lesion detection (adenomas and SSL) than patients under routine care. To our knowledge, there are no data to assess the impact of clinical research projects on quality performance in endoscopy units.

Our aim was to assess the colonoscopy quality indicators in patients who were included in a control group for an endoscopic clinical trial at our institution and compare them with a sample group from the same institution.

MATERIALS AND METHODS

Patients and Setting

We conducted a retrospective cross-sectional study comparing a colonoscopies performed in a clinical trial setting and a group of "routine" colonoscopies.

Inclusion Criteria

The inclusion criteria for the control group were similar to those for the trials with registered protocols, which included patients aged 40 to 79 undergoing outpatient colonoscopies. Bowel preparation quality was determined with the Boston Bowel Preparation Score (BBPS) and deemed adequate if at least 2 points were reached in each segment. One of the trials excluded patients with one or more segment with a BBPS below 2, but the other trial randomized patients before the colonoscopy preparation, and preparation quality was not an exclusion criterion. To control for bowel preparation quality, we decided to include only cases with BBPS scores of at least 2 in each segment.

Patients with polyposis syndromes, primary sclerosing cholangitis, inflammatory bowel disease, a personal history of colorectal cancer or surgery or failure to reach the caecum were excluded.

All patients provided informed written consent before their procedures and a specific consent form was completed for those who were participants in the trials. The Institutional

Review Board approved the collection of data for this observational study.

Case Selection

Routine colonoscopies for the control group were randomly selected from our department's database of routine colonoscopies. For the "trial group", colonoscopies were randomly selected from the control arms of two trials performed at our institution (NCT03856957 and NCT02876133). A computer-generated algorithm was created for case selection. Cases were selected from our 2019 colonoscopy database of outpatient colonoscopies performed in subjects aged 40-79 years during 2019. If the cases did not meet the study criteria, they were excluded from the selection.

In the clinical trials we defined a cut-off of 300 colonoscopies to allow the participation of an endoscopist which allowed the participation of senior endoscopists and two residents. In the control group colonoscopies from nine senior endoscopists and the same two "senior" residents were included.

Study Outcomes

The primary outcome was the pre-malignant lesion detection rate, and the secondary outcomes were the polyp detection rate, ADR, sessile serrated lesion (SSL) detection rate, number of pre-malignant lesions, adenomas and SSL per colonoscopy and number of serrated lesions >9 mm.

Sample Size Calculation and Statistical Analysis

We decided to use a 2:1 trial group to control group ratio since we already had the trial database with over 1000 cases and calculated a sample size of 294 trial colonoscopies and 147 control colonoscopies to have 80% power to detect a difference based on our own preliminary data. For the control group, we assumed a 36% ADR from our own series,[30] and for the study group, we assumed a 60% ADR based on our Endocuff trial (NCT03856957) and the recently published ADENOMA trial, an RCT also studying Endocuff.[31]

To determine the "clinical trial" effect more accurately, we adjusted the study endpoints for age, sex, bowel preparation, sedation depth and personal history of polyps using multivariate logistic regression analysis. We adjusted individually for each confounder and then tested all variables in a single model.

The mean and standard deviation are shown for continuous variables with a normal distribution. These were compared using an independent t-test. Categorical variables are presented as proportions (%) and compared with the Fisher's exact or χ^2 test. Logistic regression was used to determine the effect estimates, which are presented as odds ratios and 95% confidence intervals. Missing data were resolved by pairwise deletion. Statistical analysis was conducted with the SPSS software package, version 21 (Statistical Package for the Social Sciences, IBM Corporation, Armonk, NY, USA).

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

RESULTS

Patients

A total of 441 colonoscopies were selected, of which 294 were included in the clinical trial group and 147 were included in the control group. Baseline characteristics are depicted in Table 1.

Most baseline characteristics (age, sex, colorectal cancer family history and personal history of polyps) were similar between the two groups. Sedation was significantly different because in the clinical trials group, all cases were performed under deep sedation.

Outcomes

The study outcomes are summarized in Table 2. All lesion types were more frequently detected in the trial group. The pre-malignant lesion detection rate was 65.6% vs 44.2% (OR 2.411; 95% CI 1.608-3.614; p<0.001), the polyp detection rate was 73.8% vs 59.9% (OR 1.889; 95% CI 1.242-2.876; p=0.003), the adenoma detection rate was 62.6% vs 44.2% (OR 2.110; 95% CI

1.411-3.155; p<0.001) and the sessile serrated lesion detection rate was 17% vs 4.1% (OR 4.816; 95% CI 2.014-11.515; p<0.001). The mean number of pre-malignant and sessile serrated lesions was higher in the research group, with 1.70 vs 1.06, p=0.002 and 0.32 vs 0.06 (p=0.001) lesions per colonoscopy, respectively. The mean number of lesions (overall) was not significantly different between the groups.

In a multivariate analysis with each single potential confounder, there was no significant change in any of the study outcomes.

The effects on the main quality indicators (ADR, SSL and pre-malignant lesion detection rate) were adjusted in a single model including age, sex, sedation depth and history of polyps (Table 3). In this model, the detection odds ratios were kept at a significant level for pre-malignant lesions (OR 2.316; 95% CI 1.307-4.102; p=0.004), SSL detection rate (OR 6.810 95% IC 1.588-29.210; p=0.010) and ADR (OR 2.002; 95% IC 1.129-3.549; p=0.018).

DISCUSSION

Our study compared the main colonoscopy quality indicators in two separate groups comprising 441 colonoscopies performed at our institution. In one group, patients underwent routine colonoscopy and were not participants in any clinical trial. They were later selected, and their data were retrospectively recorded without any prior knowledge of group membership by the intervening clinical team. In the other group, we had colonoscopies that were selected from the control groups of clinical trials, where the clinical team was aware that the outcomes would be systematically recorded and analysed.

In this study, we observed higher ADR, SSLDR and lesion detection in colonoscopies that were performed in a clinical trial setting. The results showed high lesion detection rates in both groups; these rates were well above the thresholds proposed by the leading endoscopy societies (ESGE and ASGE).

CRC is a leading cancer in the Western world. Effectively increasing the ADR by just 1% has been shown to decrease CRC incidence by 3%; however, there is remarkable inter-endoscopist variability in this metric, with rates ranging between 7.4% and 52.5%.[9] There have been significant efforts to establish quality indicators to guide endoscopy practitioners in

their quest to maximize the effectiveness of colorectal cancer screening, and although it can be argued, currently, the best indicators of quality are probably adenoma detection rate and mean adenomas per colonoscopy.[16,17] The ADR is the most studied and widely accepted quality measure,[17,32] but the mean adenoma number may be more discriminative and more resistant to gaming. The SSLDR suffers from even more variability between endoscopists, as these lesions may be harder to detect than conventional adenomas.[33,34] In one study, this variability was 20-fold, ranging from 0.3% to 6.7% among endoscopists from the same group.[34] Furthermore, evidence is also increasing to support sessile serrated lesion detection as an important quality metric, especially for the proximal colon due to their association with interval cancer due to missed lesions.[35,36]

Studies have shown that when endoscopists are audited, publicly report their indicators and receive feedback, their performance increases up to 45%.[37-39] This type of intervention, if effective, is potentially more cost-effective than using artificial intelligence equipment or single-use devices such as the third eye or even the Endocuff cap. In our department, we have been interested in determining our own quality indicators and published them as a benchmark reference.[30] We have also performed several trials on colonoscopy quality in the last few years,[40] one of which is currently recruiting participants (NCT02876133). This study was initiated after we noticed high rates of detection in these trials.

We acknowledge some important limitations inherent to the study design. The endoscopists in the trial group were not aware of this particular study, but they were not blinded to the research protocols as they were aware of the trial in which they were involved. The control group data were retrospectively collected; thus, some potentially relevant confounders, such as family history of CRC or withdrawal time, were not accounted for, as the data were not available. Only in 2019 did the electronic reporting system start to automatically record the withdrawal time. Moreover, the groups were not properly matched even though the baseline characteristics were quite similar. We tried to overcome that limitation by adjusting the outcomes for known potential confounders such as age, sex and sedation. Bowel preparation was controlled with by including only colonoscopies with at least 2 BBPS points in each bowel segment. Furthermore, with the multivariate analysis, we were able to see an

association of age, male sex and personal history of polyps with higher lesion detection. The model also allows us to confirm that the association of being in a trial with higher lesion detection rates is independent of age, sex, personal history of polyps and sedation depth.

The strengths of our study include being the first to analyse the impact of participating in an endoscopy trial and showing a significant benefit of participating in clinical trials. There have been a few other studies on the impact of research in other areas, such as cancer[41,42] and women's health,[43] although these studies have had conflicting results.[44]

In conclusion, this study showed, for the first time, that being involved in research, specifically in colonoscopy clinical trials, may lead to a significant improvement in the detection of pre-malignant lesionseven if the subjects are allocated to control/placebo groups. Should our results be confirmed among other centres/study groups it could help to foster clinical research in colonoscopy quality with the added clinical benefit of decreasing CRC burden.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

No funding to declare.

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References

1. Ferlay J, Colombet M, Soerjomataram I et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019; 144: 1941-1953
2. Winawer SJ, Zauber AG, Ho MN et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993; 329: 1977-1981
3. Loberg M, Kalager M, Holme O et al. Long-term colorectal-cancer mortality after adenoma removal. N Engl J Med 2014; 371: 799-807
4. Nishihara R, Wu K, Lochhead P et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013; 369: 1095-1105
5. Schoen RE, Pinsky PF, Weissfeld JL et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012; 366: 2345-2357
6. Shaukat A, Mongin SJ, Geisser MS et al. Long-term mortality after screening for colorectal cancer. N Engl J Med 2013; 369: 1106-1114
7. Zauber AG, Winawer SJ, O'Brien MJ et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012; 366: 687-696
8. Kaminski MF, Wieszczy P, Rupinski M et al. Increased Rate of Adenoma Detection Associates With Reduced Risk of Colorectal Cancer and Death. Gastroenterology 2017; 153: 98-105
9. Corley DA, Jensen CD, Marks AR et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014; 370: 1298-1306
10. Leung WK, Lo OS, Liu KS et al. Detection of colorectal adenoma by narrow band imaging (HQ190) vs. high-definition white light colonoscopy: a randomized controlled trial. Am J Gastroenterol 2014; 109: 855-863
11. Ng SC, Tsoi KK, Hirai HW et al. The efficacy of cap-assisted colonoscopy in polyp detection and cecal intubation: a meta-analysis of randomized controlled trials. Am J Gastroenterol 2012; 107: 1165-1173
12. Gralnek IM, Siersema PD, Halpern Z et al. Standard forward-viewing colonoscopy versus full-spectrum endoscopy: an international, multicentre, randomised, tandem colonoscopy trial. Lancet Oncol 2014; 15: 353-360

13. Chung SJ, Kim D, Song JH et al. Comparison of detection and miss rates of narrow band imaging, flexible spectral imaging chromoendoscopy and white light at screening colonoscopy: a randomised controlled back-to-back study. Gut 2014; 63: 785-791
14. He X, Hang D, Wu K et al. Long-term Risk of Colorectal Cancer After Removal of Conventional Adenomas and Serrated Polyps. Gastroenterology 2020; 158: 852-861.e854
15. JE IJ, de Wit K, van der Vlugt M et al. Prevalence, distribution and risk of sessile serrated adenomas/polyps at a center with a high adenoma detection rate and experienced pathologists. Endoscopy 2016; 48: 740-746
16. Kaminski MF, Thomas-Gibson S, Bugajski M et al. Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) quality improvement initiative. Endoscopy 2017; 49: 378-397
17. Rex DK, Schoenfeld PS, Cohen J et al. Quality indicators for colonoscopy. Gastrointest Endosc 2015; 81: 31-53
18. Atkinson NSS, Ket S, Bassett P et al. Narrow-band imaging for detection of neoplasia at colonoscopy: a meta-analysis of data from individual patients in randomized controlled trials. Gastroenterology 2019; 157: 462-471
19. Pellisé M, Fernández-Esparrach G, Cárdenas A et al. Impact of wide-angle, high-definition endoscopy in the diagnosis of colorectal neoplasia: a randomized controlled trial. Gastroenterology 2008; 135: 1062-1068
20. Karsenti D, Tharsis G, Perrot B et al. Adenoma detection by Endocuff-assisted versus standard colonoscopy in routine practice: a cluster-randomised crossover trial. Gut 2020, DOI: 10.1136/gutjnl-2019-319565:
21. Ngu WS, Bevan R, Tsiamoulos ZP et al. Improved adenoma detection with Endocuff Vision: the ADENOMA randomised controlled trial. Gut 2019; 68: 280-288
22. Wang P, Berzin TM, Glissen Brown JR et al. Real-time automatic detection system increases colonoscopic polyp and adenoma detection rates: a prospective randomised controlled study. Gut 2019; 68: 1813-1819
23. Gurudu SR, Boroff ES, Crowell MD et al. Impact of feedback on adenoma detection rates: Outcomes of quality improvement program. J Gastroenterol Hepatol 2018; 33: 645-649
24. Lee SW, Chang JH, Ji JS et al. Effect of Dynamic Position Changes on Adenoma Detection During Colonoscope Withdrawal: A Randomized Controlled Multicenter Trial. Am J Gastroenterol 2016; 111: 63-69

25. Aziz M, Sharma S, Fatima R et al. How to increase proximal adenoma detection rate: a meta-analysis comparing water exchange, water immersion and air/CO(2) insufflation methods for colonoscopy. Ann Gastroenterol 2020; 33: 178-186
26. de Brouwer EJ, Arbouw ME, van der Zwet WC et al. Hyoscine N-butylbromide does not improve polyp detection during colonoscopy: a double-blind, randomized, placebo-controlled, clinical trial. Gastrointest Endosc 2012; 75: 835-840
27. Bai Y, Fang J, Zhao SB et al. Impact of preprocedure simethicone on adenoma detection rate during colonoscopy: a multicenter, endoscopist-blinded randomized controlled trial. Endoscopy 2018; 50: 128-136
28. Triantafyllou K, Gkolfakis P, Tziatzios G et al. Effect of Endocuff use on colonoscopy outcomes: a systematic review and meta-analysis. World J Gastroenterol 2019; 25: 1158-1170
29. Desai M, Viswanathan L, Gupta N et al. Impact of electronic chromoendoscopy on adenoma miss rates during colonoscopy: a systematic review and meta-analysis. Dis Colon Rectum 2019; 62: 1124-1134
30. Oliveira Ferreira A, Fidalgo C, Palmela C et al. Adenoma detection rate: I will show you mine if you show me yours. GE Port J Gastroenterol 2017; 24: 61-67
31. Ngu WS, Bevan R, Tsiamoulos ZP et al. Improved adenoma detection with Endocuff Vision: the ADENOMA randomised controlled trial. Gut 2019; 68: 280-288
32. Ponugoti P, Lin J, Odze R et al. Prevalence of sessile serrated adenoma/polyp in hyperplastic-appearing diminutive rectosigmoid polyps. Gastrointest Endosc 2017; 85: 622-627
33. Kahi CJ, Hewett DG, Norton DL et al. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. Clin Gastroenterol Hepatol 2011; 9: 42-46
34. Hetzel JT, Huang CS, Coukos JA et al. Variation in the detection of serrated polyps in an average risk colorectal cancer screening cohort. Am J Gastroenterol 2010; 105: 2656-2664
35. Arain MA, Sawhney M, Sheikh S et al. CIMP status of interval colon cancers: another piece to the puzzle. Am J Gastroenterol 2010; 105: 1189-1195
36. Farrar WD, Sawhney MS, Nelson DB et al. Colorectal cancers found after a complete colonoscopy. Clin Gastroenterol Hepatol 2006; 4: 1259-1264
37. Kahi CJ, Ballard D, Shah AS et al. Impact of a quarterly report card on colonoscopy quality measures. Gastrointest Endosc 2013; 77: 925-931
38. Abdul-Baki H, Schoen RE, Dean K et al. Public reporting of colonoscopy quality is associated with an increase in endoscopist adenoma detection rate. Gastrointest Endosc 2015; 82: 676-682

39. Gurudu SR, Boroff ES, Crowell MD et al. Impact of feedback on adenoma detection rates: outcomes of quality improvement program. J Gastroenterol Hepatol 2018; 33: 645-649
40. Ferreira AO, Torres J, Barjas E et al. Non-anesthesiologist administration of propofol sedation for colonoscopy is safe in low risk patients: results of a noninferiority randomized controlled trial. Endoscopy 2016; 48: 747-753
41. Medeiros BC, Othus M, Tallman MS et al. The relationship between clinical trial accrual volume and outcomes in acute myeloid leukemia: a SWOG/ECOG-ACRIN study (S0106 and E1900). Leuk Res 2019; 78: 29-33
42. Du Bois A, Rochon J, Lamparter C et al. Pattern of care and impact of participation in clinical studies on the outcome in ovarian cancer. Int J Gynecol Cancer 2005; 15: 183-191
43. Nijjar SK, D'Amico MI, Wimalaweera NA et al. Participation in clinical trials improves outcomes in women's health: a systematic review and meta-analysis. BJOG 2017; 124: 863-871
44. Khoja L, Horsley L, Heesters A et al. Does clinical trial participation improve outcomes in patients with ovarian cancer? ESMO Open 2016; 1: e000057

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TABLES

Table 1. Baseline characteristics of the study population

	Trial Group (n=294)	Control Group (n=147)	p-value
Age, y	62.16 (9.81)	61.97 (9.97)	0.802
Male sex, n (%)	161 (54.8)	70 (47.6)	0.157
CRC family history, n (%)	65 (22.4)	26 (18.1)	0.294
Previous colonoscopy, n (%)	133 (45.4)	74 (50.7)	0.295
Personal history of polyps, n (%)	87 (29.7)	44 (30.3)	0.888
Deep sedation, n (%)	294 (100)	65 (44.2)	0.001
Conscious sedation, n (%)		62 (42.2)	
No sedation, n (%)		20 (13.6)	
Indication			0.050
• Screening	53 (17.3)	24 (16.3)	
• FOBT/diagnostic	214 (69.9)	89 (60.5)	
• Surveillance	39 (12.7)	34 (23.1)	

Table 2. Primary and secondary outcomes

	Trial Group (n=316)	Control Group (n=182)	p-value
Mean polyp number (se)	2.21 (0.14)	1.74 (0.12)	0.062
Mean pre-malignant lesion number (se)	1.70 (0.12)	1.06 (0.16)	0.002
Mean adenoma number (se)	1.38 (0.10)	1.00 (0.15)	0.032
Mean SSL number (se)	0.32 (0.02)	0.06 (0.02)	0.001
Mean number of serrated lesions >9 mm (se)	0.06 (0.019)	0.02 (0.015)	0.158
Polyp detection rate, %	73.8	59.9	0.003
Pre-malignant lesion detection rate, %	65.6	44.2	<0.001
Adenoma detection rate, %	62.6	44.2	0.0002
Sessile serrated lesion detection rate, %	17.0	4.1	0.0001

Table 3. Logistic regression to control for potential confounders for pre-malignant lesion detection

Variables	Odds ratio	Robust standard errors	p
Trial group	2.316 (1.307-4.102)	0.292	0.004***
Age	1.043 (1.021-1.065)	0.011	0.0001***
Sex:			
female	0.478 (0.315-0.725)	0.213	0.001***
Sedation:			
no	0.892 (0.447-1.779)	0.352	0.745
Polyp history:			
yes	1.610 (1.005-2.578)	0.240	0.048*
Wald χ^2 test	*54.436****		
Pseudo R^2	*0.158*		

*** denote p-values < 0.01, ** denotes p-value < 0.05.

CHAPTER IV.

DISCUSSION

Our works revolved around two dimensions of colonoscopy quality. The first two studies were dedicated to sedation and monitoring practices in gastrointestinal endoscopy. The third study was an audit performed at our unit to establish performance indicators and benchmarks for other units and for the future of our practice. The two detection trials were an attempt to improve the awareness and the identification of a subset of pre-malignant lesions: the sessile serrated lesions. Although the studies did not have positive conclusions on the usage of NBI and EV, there was an overall (including the control group) improved detection when compared to the benchmark set in our previous study. This was probably the result of increased endoscopist and pathologist awareness for this type of lesions.

In the last study we determined that participation in colonoscopy prospective studies is associated to increased pathology identification and thus such studies should be pursued by organizations with interest in colorectal cancer screening.

a. SEDATION IN COLONOSCOPY

In the first manuscript we reported the results of a Portuguese survey performed in 2014. The survey had a 26% response rate. The respondents worked at both private and public institutions and reported differences in the sedation type according to their workplace with propofol being used in 55% in the private practice scenario and 33% ($p<0.0001$) in public hospitals, where traditional sedation is also frequently used, even though propofol is associated with higher satisfaction scores. NAAP was very rarely reported with only 3.6% of respondents reporting its' use, mostly because of a lack of training and medico-legal issues, similarly to the American, Italian and Greek survey results.

The accuracy of this study was limited by the 26% response rate but this proportion is undervalued since the total number considered was the pool of 490 associates of the *Sociedade Portuguesa de Gastrenterologia* which included doctors who were retired or did not perform endoscopy at all (hepatologists, surgeons or pathologists).

Since 2014 the landscape has most certainly changed. The volume of colonoscopy in the private sector increased significantly and the National Health Service started to compensate the anaesthesia services in the private sector, this alteration probably led to a significantly increased utilization of anaesthesiologist directed propofol sedation.

In the second study we performed a randomized trial to evaluate the safety and feasibility of NAAP in Portugal. NAAP has been shown to be safe in large observational

studies [113,118] and is routinely performed in a few European countries like Germany, Austria, Denmark and in some centers in Spain, Italy and Greece but it is very uncommon in Portugal, as we have shown. In our study, we included 277 patients undergoing colonoscopy and assigned them to a group of NAAP and to a control group with an anaesthesiologist. The groups were well balanced and apart from a lower incidence of bradycardia in the NAAP group (due to higher use of butylscpolamine) there was no difference in the overall incidence of adverse events, which was our primary endpoint. The recovery time was lower in the NAAP group (58 vs 67 min, p=0.032) and the adenoma detection rates were similar between groups (28.4% vs 23.2%, p=0.331). The longer recovery time was associated with the use of midazolam and/or alfentanyl.

These results are in line to the previous RCT on NAAP with 180 patients [116] and to a recently published third one with 630 patients [153]. All three trials showed non-inferiority in safety, as measured by the incidence of adverse events, in patient satisfaction scores and in the adenoma detection rate when using NAAP.

Several trials and meta-analysis have also compared the use of propofol and traditional sedation, which is usually a combination of a short acting benzodiazepine like midazolam and an opioid like fentanyl. There is a small benefit in favour of propofol sedation with higher patient satisfaction, cecal intubation rate, recovery time and a lower incidence of complications [154,155].

Despite this strong evidence, it must be acknowledged that randomized trials have an important limitation when addressing the safety issue since hard endpoints like death or neurologic disability are exceedingly rare in routine endoscopic procedures which would lead to unfeasible sample sizes in excess of 100.000 procedures [95,113].

Nevertheless, the existing data support the widespread use of propofol which has been adopted in most countries as the most commonly used agent for sedation in endoscopy.

b. COLONOSCOPY AUDITING

In the third study we performed a review of 3 years of activity in our Endoscopy Unit at Hospital Beatriz Ângelo. Our aim was to know how effective our colonoscopies were and to establish benchmarks against which other units and even our future activity could be compared. Another aim was to allow the measurement of specific quality improvement interventions over time. We analyzed 654 screening and FOBT positive

colonoscopies with an overall adenoma detection rate of 36% (95%CI 32-39) and 0.66 adenomas per colonoscopy. The identification of a low SSL detection of 1% led to multidisciplinary discussion with the pathologists and an increased awareness which improved our sensitivity for these lesions in our most recent reports (up to 7%). Another important indicator that was deemed subpar was the bowel preparation with almost a quarter of colonoscopies classified as having a poor preparation and this in turn is known to be associated with a lower cecal intubation rate, a lower adenoma detection rate, an increased incidence of adverse events and repeat procedures[156]. After this study we renewed our preparation leaflets and adopted split-dose regimens which are advocated by major guidelines but was slowly adopted due to fear of aspiration, fecal incontinence and low patient education [157]. We also changed the colonoscopy report in order to include a validated bowel preparation score – the Boston Bowel Preparation Score.

c. Improving Sessile Serrated Lesions detection

We evaluated the utility of NBI and Endocuff Vision in routine/screening colonoscopy. Since these technologies were previously studied for adenoma detection and since we were interested in studying and improving our own performance for the detection of serrated lesions, we decided to design two trials specifically with SSL detection as the primary endpoints.

Our NBI study was halted due to the COVID pandemic but we were able to randomize a total of 782 patients to NBI or white light inspection during withdrawal and looked into the detection of SSL adenomas and cancer. This study failed to show any significant differences in the detection of these lesions even though it increased the inspection time by a mean of 85 seconds (p=0.004), probably because NBI inspection needs more work to wash and clean all debris and achieve a better bowel preparation, as even a small amount of clear fluid may impair mucosal inspection. For the primary endpoint we used a combination of histological diagnosed of sessile serrated lesions with or without dysplasia and centimetric hyperplasic polyps to overcome pathological underdiagnosis. In a previous trial by Douglas Rex [76] they included all hyperplastic lesions and although this decision would increase the power of the study, the clinical significance of such lesions would be debatable.

There are now several RCTs and meta-analysis of RCTs studying the role of NBI for the detection of adenomasm[74] and serrated lesionsm[150] and there seems to be a small benefit that only becomes apparent when pooling the studies and looking into

the subgroup using second generation NBI and patients with optimal bowel preparation. Even though our trial used second generation NBI equipment, the lack of difference between groups and the added procedural time suggest NBI should be used as add on to white light and not the main examination light during withdrawal.

In the Endocuff Vision study we used the same composite endpoint of the mean number of sessile serrated lesions and hyperplastic polyps >9 mm per colonoscopy. There was a non-significant higher number of lesions in the EV group (0.02 vs 0.06, p=0.131) and no differences in any of the other detection metrics (PDR, ADR, MAPC, SSL detection rate) nor in the inspection or procedure times. In the large EV trial ADENOMA (n=1772), there was a significant higher detection of both adenomas and SSL, however this difference was only apparent in the screening subgroup (n=797). EV helps to detect lesions behind folds and for this reason it was shown to be more effective the left colon. Sessile serrated lesions are preferentially located in the right colon and essentially hard to detect due to two reasons: they may be completely flat and present very subtle features which make them similar to the underlying normal colonic mucosa. A combination of EV and endoscopic image enhancement could be more effective to increase the sensitivity for these lesions.

Based on our studies and in the currently available evidence it can be suggested to use routinely for screening colonoscopy and consider using NBI when the bowel preparation is optimal and especially in the right colon.

d. IMPACT OF RESEARCH ON COLONOSCOPY QUALITY

The last study was motivated by our observation that over time the detection of pathology in the colonoscopies being performed at our institution was increasing substantially from an ADR of 36% in 2012-2014 to 65% in the Endocuff study in 2019. We hypothesized that this could be due to technological and training issues that changed over the 5-year period or it could also be because of the lack of blinding of the endoscopists participating in trials' colonoscopies, since it has been shown that endoscopists perform better when they know they are being audited [158].

To evaluate this effect, we designed a study to determine the main quality indicators in a group of colonoscopies included in the NBI and EV trials and a control group selected from a population with the same inclusion criteria and with colonoscopies performed by the same endoscopists within the same timeframe (2019). We included

441 colonoscopies in a 2:1 ratio and observed higher ADR, SSLDR and lesion detection in colonoscopies that were performed in a clinical trial setting.

We must recognize that such study design has some relevant limitations. The first one is that the endoscopists in the trial knew they were being observed and their performance was under direct scrutiny. Secondly, the control group data was retrospectively collected and as such some potential confounders such as family history of CRC and withdrawal time were not accounted for. Another limitation was the lack of a proper matching between groups but we tried to overcome this situation by applying a multivariate analysis with known potential confounders.

Still, this study is the first to evaluate the impact of research on colonoscopy quality and it suggests that there was a significant clinical benefit for the patients that were included in these trials.

This study should prompt endoscopy units to pursue excellence and motivate practitioners to evaluate key performance indicators and to set up interventions to improve what is the ultimate goal of colonoscopy: detection and resection of pre-malignant lesions in order to decrease CRC burden.

CHAPTER V.

CONCLUSION AND FUTURE RESEARCH

Colonoscopy is of paramount importance for colorectal cancer screening and sedation is an increasingly important part of the procedure. Most colonoscopies in Portugal are performed with traditional sedation (midazolam alone or with an opioid) or anesthesiologist directed propofol sedation but propofol is the preferred agent for Portuguese endoscopists. NAAP is virtually non-existent due to lack of training and medico-legal issues regarding the administration of propofol.

The administration of propofol during routine colonoscopies in low-risk patients allows high quality examinations and can be safely performed by a team including an endoscopist and nurses with adequate training in sedation and airway management. Propofol is the agent of choice for patients and endoscopists and increasing its availability may improve the willingness of the population to undertake endoscopic screening and surveillance.

The auditing of colonoscopy quality indicators is a useful tool to assess the effectiveness, establish benchmarks, identify subpar indicators and design proven interventions to improve the effectiveness and safety of the colonoscopy. Performance indicators such as the quality of bowel preparation, sedation utilization, patient satisfaction, pathology detection and resection technique are highly variable and may be improved. Endoscopy units should therefore establish protocols to maintain continuous auditing activity in order to promote the improvement of the endoscopists activity and maximize the outcomes of screening.

Colonoscopy and colonoscopes have had a remarkable evolution over the last few decades. Several devices and techniques have been developed and evaluated in order to improve the pre-malignant lesions detection yield of the colonoscopy. Endocuff Vision is one of these devices and has been shown to improve the detection of adenomas. We performed a study which only showed a non-significant trend towards higher detection of sessile serrated lesions when using the EV distal attachment. EV may be a useful adjunct since it increases adenoma detection rates with no significant downsides.

NBI is a simple to use advanced imaging technique but the studies on pathology detection have had conflicting results. We performed a large trial that failed to show a difference in the detection of both sessile serrated lesions and adenomas. The use of NBI was associated to a small increase in the procedural time with no added benefit. NBI should be reserved for patients with very good bowel preparation and in conjunction with high-definition white light inspection of the mucosa.

Participating in research studies is an act of generosity by the individuals and in our data we were able to determine that the participation in prospective colonoscopy studies in which the endoscopists are being actively audited, leads to an increase in the detection of pre-malignant lesions. Endoscopy units should promote research in colonoscopy quality with the added benefit of improving the performance indicators and minimize the future burden of colorectal cancer which is our ultimate goal.

Our results are important to raise societal awareness for colorectal cancer screening and also for gastroenterologists and policy makers to understand that colonoscopy not only is effective and safe as a means for the prevention and early diagnosis of a major public health issue in Portugal, but also that quality is multi-dimensional and highly variable. Units should be incentivized to design and establish interventions to improve the effectiveness of colonoscopy. By having a genuine interest and by working together (gastroenterologists, anesthesiologists, pathologists and nurses), performing research and auditing the results it is possible to maximize the outcomes of our daily practice.

Future Research

Further studies are needed to keep up with the ongoing evolution in endoscopy.

Since our national survey, the landscape of sedation has probably changed considerably with a more widespread adoption of propofol based sedation. For this reason, we have started to work on new survey which is currently underway and will allow us to understand the evolution of the last few years.

New devices and technological advances keep pushing the quality indicators to new heights which were unrealistic a couple of decades ago. Imaging, chromoendoscopy improvements and the recently introduced computer-aided polyp detection (artificial intelligence) equipments which are a significant improvement in the identification of neoplastic lesions [159]. With an increasingly higher sensitivity we will identify smaller lesions and very subtle lesions that were almost invisible when trials like the National Polyp Study were performed. Therefore, it is of the utmost importance to determine whether these lesions are clinically relevant, how should they affect surveillance schedules and what is the impact of their removal in what matters most: CRC incidence and mortality.

In the future, it will be important to evaluate the value of the key performance measures as the adenoma detection rate becomes less discriminative. Possible

performance indicators to consider and evaluate include the mean number of adenomas per colonoscopy, adenomas per positive colonoscopy or the inclusion of sessile serrated lesions detection in a combined metric. It will be possible and desirable to refine the risk stratification of the patients and establish personalized indicator thresholds. Apart from this, it will also be relevant to study the performance measures and pathology identification measures outside the setting of colorectal cancer screening.

Although there has been a significant evolution in recent decades that led to the widespread acceptance of colonoscopy as a safe, painless and cost-effective screening procedure, there is still room to further improve the outcomes as the cancer of the colon and rectum remains a top cancer in most western countries.

Bibliography

1. Ferlay J, Colombet M, Soerjomataram I et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019; 144: 1941-1953
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69: 7-34
3. Edwards BK, Ward E, Kohler BA et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 2010; 116: 544-573
4. Zauber AG, Winawer SJ, O'Brien MJ et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012; 366: 687-696
5. Messersmith WA. NCCN Guidelines Updates: Management of Metastatic Colorectal Cancer. J Natl Compr Canc Netw 2019; 17: 599-601
6. [Anonymous]. AGA institute guidelines for colonoscopy surveillance after cancer resection: clinical decision tool. Gastroenterology 2014; 146: 1413-1414
7. Segnan N, Patnick J, von Karsa L. European guidelines for quality assurance in colorectal cancer screening and diagnosis – First edition. In. Luxembourg: Publications Office of the European Union; 2010
8. Shaukat A, Kahi CJ, Burke CA et al. ACG Clinical Guidelines: Colorectal Cancer Screening 2021. Am J Gastroenterol 2021; 116: 458-479
9. Wolf AMD, Fontham ETH, Church TR et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin 2018; 68: 250-281
10. Roquette R, Painho M, Nunes B. Geographical patterns of the incidence and mortality of colorectal cancer in mainland Portugal municipalities (2007-2011). BMC Cancer 2019; 19: 512
11. Siegel RL, Jemal A. Percentage of colorectal cancer diagnosed in adults aged younger than 50 years. Cancer 2016; 122: 1462-1463
12. Araghi M, Soerjomataram I, Jenkins MA et al. Global trends in colorectal cancer mortality: projections to the year 2035. International Journal of Cancer 2019; 144:
13. [Anonymous]. The global, regional, and national burden of colorectal cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2019; 4: 913-933
14. Chan DS, Lau R, Aune D et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PLoS One 2011; 6: e20456
15. Tabung FK, Brown LS, Fung TT. Dietary Patterns and Colorectal Cancer Risk: A Review of 17 Years of Evidence (2000-2016). Curr Colorectal Cancer Rep 2017; 13: 440-454
16. Song M, Chan AT. Environmental Factors, Gut Microbiota, and Colorectal Cancer Prevention. Clin Gastroenterol Hepatol 2019; 17: 275-289
17. Chapelle N, Martel M, Toes-Zoutendijk E et al. Recent advances in clinical practice: colorectal cancer chemoprevention in the average-risk population. Gut 2020; 69: 2244-2255
18. Eheman C, Henley SJ, Ballard-Barbash R et al. Annual Report to the Nation on the status of cancer, 1975-2008, featuring cancers associated with excess weight and lack of sufficient physical activity. Cancer 2012; 118: 2338-2366
19. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990; 61: 759-767
20. Carethers JM, Jung BH. Genetics and Genetic Biomarkers in Sporadic Colorectal Cancer. Gastroenterology 2015; 149: 1177-1190.e1173
21. Strum WB. Colorectal Adenomas. N Engl J Med 2016; 374: 1065-1075
22. East JE, Vieth M, Rex DK. Serrated lesions in colorectal cancer screening: detection, resection, pathology and surveillance. Gut 2015; 64: 991-1000
23. East JE, Atkin WS, Bateman AC et al. British Society of Gastroenterology position statement on serrated polyps in the colon and rectum. Gut 2017; 66: 1181-1196
24. Hazewinkel Y, López-Cerón M, East JE et al. Endoscopic features of sessile serrated adenomas: validation by international experts using high-resolution white-light endoscopy and narrow-band imaging. Gastrointest Endosc 2013; 77: 916-924
25. Haque TR, Bradshaw PT, Crockett SD. Risk factors for serrated polyps of the colorectum. Dig Dis Sci 2014; 59: 2874-2889
26. Kahi CJ, Li X, Eckert GJ et al. High colonoscopic prevalence of proximal colon serrated polyps in average-risk men and women. Gastrointest Endosc 2012; 75: 515-520

27. de Wijkerslooth TR, Stoop EM, Bossuyt PM et al. Differences in proximal serrated polyp detection among endoscopists are associated with variability in withdrawal time. Gastrointest Endosc 2013; 77: 617-623
28. Heresbach D, Barrioz T, Lapalus MG et al. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies. Endoscopy 2008; 40: 284-290
29. Payne SR, Church TR, Wandell M et al. Endoscopic detection of proximal serrated lesions and pathologic identification of sessile serrated adenomas/polyps vary on the basis of center. Clin Gastroenterol Hepatol 2014; 12: 1119-1126
30. Lieberman DA, Rex DK, Winawer SJ et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012; 143: 844-857
31. Winawer SJ, Zauber AG, Ho MN et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993; 329: 1977-1981
32. Shaukat A, Mongin SJ, Geisser MS et al. Long-term mortality after screening for colorectal cancer. N Engl J Med 2013; 369: 1106-1114
33. Nishihara R, Wu K, Lochhead P et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013; 369: 1095-1105
34. Loberg M, Kalager M, Holme O et al. Long-term colorectal-cancer mortality after adenoma removal. N Engl J Med 2014; 371: 799-807
35. Corley DA, Jensen CD, Marks AR et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med 2014; 370: 1298-1306
36. Kaminski MF, Regula J, Kraszewska E et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 2010; 362: 1795-1803
37. Qaseem A, Crandall CJ, Mustafa RA et al. Screening for Colorectal Cancer in Asymptomatic Average-Risk Adults: A Guidance Statement From the American College of Physicians. Ann Intern Med 2019; 171: 643-654
38. Rex DK, Boland CR, Dominitz JA et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients From the U.S. Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2017; 153: 307-323
39. von Karsa L, Patnick J, Segnan N et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. Endoscopy 2013; 45: 51-59
40. Rex DK, Boland CR, Dominitz JA et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2017; 112: 1016-1030
41. Quintero E, Castells A, Bujanda L et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012; 366: 697-706
42. Allison JE, Sakoda LC, Levin TR et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst 2007; 99: 1462-1470
43. Lin JS, Perdue LA, Henrikson NB et al. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama 2021; 325: 1978-1998
44. Imperiale TF, Ransohoff DF, Itzkowitz SH et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014; 370: 1287-1297
45. Johnson CD, Chen MH, Toledano AY et al. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med 2008; 359: 1207-1217
46. Kim DH, Pickhardt PJ, Taylor AJ et al. CT colonography versus colonoscopy for the detection of advanced neoplasia. N Engl J Med 2007; 357: 1403-1412
47. Cotton PB, Durkalski VL, Pineau BC et al. Computed tomographic colonography (virtual colonoscopy): a multicenter comparison with standard colonoscopy for detection of colorectal neoplasia. Jama 2004; 291: 1713-1719
48. Cash BD, Fleisher MR, Fern S et al. Multicentre, prospective, randomised study comparing the diagnostic yield of colon capsule endoscopy versus CT colonography in a screening population (the TOPAZ study). Gut 2021; 70: 2115-2122

49. Pickhardt PJ, Hassan C, Halligan S et al. Colorectal cancer: CT colonography and colonoscopy for detection--systematic review and meta-analysis. Radiology 2011; 259: 393-405
50. Rex DK, Adler SN, Aisenberg J et al. Accuracy of capsule colonoscopy in detecting colorectal polyps in a screening population. Gastroenterology 2015; 148: 948-957.e942
51. Van Gossum A, Munoz-Navas M, Fernandez-Urien I et al. Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. N Engl J Med 2009; 361: 264-270
52. Holme Ø, Schoen RE, Senore C et al. Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials. Bmj 2017; 356: i6673
53. Schoen RE, Pinsky PF, Weissfeld JL et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012; 366: 2345-2357
54. Segnan N, Armaroli P, Bonelli L et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. J Natl Cancer Inst 2011; 103: 1310-1322
55. Atkin WS, Edwards R, Kralj-Hans I et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 2010; 375: 1624-1633
56. Jodal HC, Helsingen LM, Anderson JC et al. Colorectal cancer screening with faecal testing, sigmoidoscopy or colonoscopy: a systematic review and network meta-analysis. BMJ Open 2019; 9: e032773
57. Rabeneck L, Paszat LF, Saskin R et al. Association between colonoscopy rates and colorectal cancer mortality. Am J Gastroenterol 2010; 105: 1627-1632
58. Brenner H, Chang-Claude J, Jansen L et al. Reduced risk of colorectal cancer up to 10 years after screening, surveillance, or diagnostic colonoscopy. Gastroenterology 2014; 146: 709-717
59. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. Bmj 2014; 348: g2467
60. Rex DK, Cutler CS, Lemmel GT et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 1997; 112: 24-28
61. Kaminski MF, Wieszczy P, Rupinski M et al. Increased Rate of Adenoma Detection Associates With Reduced Risk of Colorectal Cancer and Death. Gastroenterology 2017; 153: 98-105
62. Aziz M, Sharma S, Fatima R et al. How to increase proximal adenoma detection rate: a meta-analysis comparing water exchange, water immersion and air/CO(2) insufflation methods for colonoscopy. Ann Gastroenterol 2020; 33: 178-186
63. Rajasekhar PT, Rees CJ, Bramble MG et al. A multicenter pragmatic study of an evidence-based intervention to improve adenoma detection: the Quality Improvement in Colonoscopy (QIC) study. Endoscopy 2015; 47: 217-224
64. Brenner H, Altenhofen L, Kretschmann J et al. Trends in Adenoma Detection Rates During the First 10 y of the German Screening Colonoscopy Program. Gastroenterology 2015, DOI: 10.1053/j.gastro.2015.04.012:
65. Rex DK, Bond JH, Winawer S et al. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2002; 97: 1296-1308
66. Kaminski MF, Thomas-Gibson S, Bugajski M et al. Performance measures for lower gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative. Endoscopy 2017; 49: 378-397
67. Saini SD, Adams MA, Brill JV et al. Colorectal Cancer Screening Quality Measures: Beyond Colonoscopy. Clin Gastroenterol Hepatol 2016; 14: 644-647
68. Rex DK, Schoenfeld PS, Cohen J et al. Quality indicators for colonoscopy. Gastrointest Endosc 2015; 81: 31-53
69. Fedewa SA, Anderson JC, Robinson CM et al. Prevalence of 'one and done' in adenoma detection rates: results from the New Hampshire Colonoscopy Registry. Endosc Int Open 2019; 7: E1344-e1354

70. Ladabaum U, Shepard J, Mannalithara A. Adenoma and Serrated Lesion Detection by Colonoscopy Indication: The ADR-ESS (ADR Extended to all Screening/Surveillance) Score. Clin Gastroenterol Hepatol 2021; 19: 1873-1882
71. Leung WK, Lo OS, Liu KS et al. Detection of colorectal adenoma by narrow band imaging (HQ190) vs. high-definition white light colonoscopy: a randomized controlled trial. Am J Gastroenterol 2014; 109: 855-863
72. Hazewinkel Y, Tytgat KM, van Leerdam ME et al. Narrow-band imaging for the detection of polyps in patients with serrated polyposis syndrome: a multicenter, randomized, back-to-back trial. Gastrointest Endosc 2014, DOI: 10.1016/j.gie.2014.06.043:
73. Chung SJ, Kim D, Song JH et al. Comparison of detection and miss rates of narrow band imaging, flexible spectral imaging chromoendoscopy and white light at screening colonoscopy: a randomised controlled back-to-back study. Gut 2014; 63: 785-791
74. Atkinson NSS, Ket S, Bassett P et al. Narrow-Band Imaging for Detection of Neoplasia at Colonoscopy: A Meta-analysis of Data From Individual Patients in Randomized Controlled Trials. Gastroenterology 2019; 157: 462-471
75. Kaminski MF, Hassan C, Bisschops R et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2014; 46: 435-449
76. Rex DK, Clodfelter R, Rahmani F et al. Narrow-band imaging versus white light for the detection of proximal colon serrated lesions: a randomized, controlled trial. Gastrointest Endosc 2015, DOI: 10.1016/j.gie.2015.03.1915:
77. Wang D, Chen C, Chen J et al. The use of propofol as a sedative agent in gastrointestinal endoscopy: a meta-analysis. PLoS One 2013; 8: e53311
78. Singh H, Poluha W, Cheung M et al. Propofol for sedation during colonoscopy. Cochrane Database Syst Rev 2008, DOI: 10.1002/14651858.CD006268.pub2: CD006268
79. Bannert C, Reinhart K, Dunkler D et al. Sedation in screening colonoscopy: impact on quality indicators and complications. Am J Gastroenterol 2012; 107: 1837-1848
80. Tox U, Schumacher B, Toermer T et al. Propofol sedation for colonoscopy with a new ultrathin or a standard endoscope: a prospective randomized controlled study. Endoscopy 2013; 45: 439-444
81. Othman MO, Bradley AG, Choudhary A et al. Variable stiffness colonoscope versus regular adult colonoscope: meta-analysis of randomized controlled trials. Endoscopy 2009; 41: 17-24
82. Wu J, Hu B. The role of carbon dioxide insufflation in colonoscopy: a systematic review and meta-analysis. Endoscopy 2012; 44: 128-136
83. Leung FW, Amato A, Ell C et al. Water-aided colonoscopy: a systematic review. Gastrointest Endosc 2012; 76: 657-666
84. Firth JD. An anesthetic technique for oral endoscopy. Anesth Analg 1960; 39: 175-179
85. Ticktin HE, Trujillo NP. Evaluation of diazepam for pre-endoscopy medication. Am J Dig Dis 1965; 10: 979-984
86. Cole SG, Brozinsky S, Isenberg JI. Midazolam, a new more potent benzodiazepine, compared with diazepam: a randomized, double-blind study of preendoscopic sedatives. Gastrointest Endosc 1983; 29: 219-222
87. Arrowsmith JB, Gerstman BB, Fleischer DE et al. Results from the American Society for Gastrointestinal Endoscopy/U.S. Food and Drug Administration collaborative study on complication rates and drug use during gastrointestinal endoscopy. Gastrointest Endosc 1991; 37: 421-427
88. Gepts E, Claeys MA, Camu F et al. Infusion of propofol ('Diprivan') as sedative technique for colonoscopies. Postgrad Med J 1985; 61 Suppl 3: 120-126
89. Kanto J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. Clin Pharmacokinet 1989; 17: 308-326
90. Bo LL, Bai Y, Bian JJ et al. Propofol vs traditional sedative agents for endoscopic retrograde cholangiopancreatography: a meta-analysis. World J Gastroenterol 2011; 17: 3538-3543
91. McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. Gastrointest Endosc 2008; 67: 910-923

92. Qadeer MA, Vargo JJ, Khandwala F et al. Propofol versus traditional sedative agents for gastrointestinal endoscopy: a meta-analysis. Clin Gastroenterol Hepatol 2005; 3: 1049-1056
93. Garewal D, Powell S, Milan SJ et al. Sedative techniques for endoscopic retrograde cholangiopancreatography. Cochrane Database Syst Rev 2012; 6: CD007274
94. Bielawska B, Day AG, Lieberman DA et al. Risk factors for early colonoscopic perforation include non-gastroenterologist endoscopists: a multivariable analysis. Clin Gastroenterol Hepatol 2014; 12: 85-92
95. Cooper GS, Kou TD, Rex DK. Complications following colonoscopy with anesthesia assistance: a population-based analysis. JAMA Intern Med 2013; 173: 551-556
96. Adeyemo A, Bannazadeh M, Riggs T et al. Does sedation type affect colonoscopy perforation rates? Dis Colon Rectum 2014; 57: 110-114
97. Vargo JJ, DeLegge MH, Feld AD et al. Multisociety sedation curriculum for gastrointestinal endoscopy. Gastroenterology 2012; 143: e18-41
98. Dumonceau JM, Riphaus A, Aparicio JR et al. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology Guideline: Non-anesthesiologist administration of propofol for GI endoscopy. Endoscopy 2010; 42: 960-974
99. Riphaus A, Wehrmann T, Weber B et al. [S3-guidelines--sedation in gastrointestinal endoscopy]. Z Gastroenterol 2008; 46: 1298-1330
100. Byrne MF, Chiba N, Singh H et al. Propofol use for sedation during endoscopy in adults: a Canadian Association of Gastroenterology position statement. Can J Gastroenterol 2008; 22: 457-459
101. Schreiber F. Austrian Society of Gastroenterology and Hepatology (OGGH)--guidelines on sedation and monitoring during gastrointestinal endoscopy. Endoscopy 2007; 39: 259-262
102. Riphaus A, Macias-Gomez C, Deviere J et al. Propofol, the preferred sedation for screening colonoscopy, is underused. Results of an international survey. Dig Liver Dis 2012; 44: 389-392
103. Hassan C, Rex DK, Cooper GS et al. Endoscopist-directed propofol administration versus anesthesiologist assistance for colorectal cancer screening: a cost-effectiveness analysis. Endoscopy 2012; 44: 456-464
104. Cohen LB, Wecsler JS, Gaetano JN et al. Endoscopic sedation in the United States: results from a nationwide survey. Am J Gastroenterol 2006; 101: 967-974
105. Liu H, Waxman DA, Main R et al. Utilization of anesthesia services during outpatient endoscopies and colonoscopies and associated spending in 2003-2009. Jama 2012; 307: 1178-1184
106. Inadomi JM, Gunnarsson CL, Rizzo JA et al. Projected increased growth rate of anesthesia professional-delivered sedation for colonoscopy and EGD in the United States: 2009 to 2015. Gastrointest Endosc 2010; 72: 580-586
107. Rex DK. Effect of the Centers for Medicare & Medicaid Services policy about deep sedation on use of propofol. Ann Intern Med 2011; 154: 622-626
108. Ladas SD, Aabakken L, Rey JF et al. Use of sedation for routine diagnostic upper gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy Survey of National Endoscopy Society Members. Digestion 2006; 74: 69-77
109. Heuss LT, Froehlich F, Beglinger C. Nonanesthesiologist-administered propofol sedation: from the exception to standard practice. Sedation and monitoring trends over 20 years. Endoscopy 2012; 44: 504-511
110. Riphaus A, Geist F, Wehrmann T. Endoscopic sedation and monitoring practice in Germany: re-evaluation from the first nationwide survey 3 years after the implementation of an evidence and consent based national guideline. Z Gastroenterol 2013; 51: 1082-1088
111. Slagelse C, Vilmann P, Hornslet P et al. Nurse-administered propofol sedation for gastrointestinal endoscopic procedures: first Nordic results from implementation of a structured training program. Scand J Gastroenterol 2011; 46: 1503-1509
112. Paspatis GA, Manolaraki MM, Tribonias G et al. Endoscopic sedation in Greece: results from a nationwide survey for the Hellenic Foundation of gastroenterology and nutrition. Dig Liver Dis 2009; 41: 807-811

113. Rex DK, Deenadayalu VP, Eid E et al. Endoscopist-directed administration of propofol: a worldwide safety experience. Gastroenterology 2009; 137: 1229-1237; quiz 1518-1229
114. Dumonceau JM, Riphaus A, Beilenhoff U et al. European curriculum for sedation training in gastrointestinal endoscopy: position statement of the European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA). Endoscopy 2013; 45: 496-504
115. Ferreira AO, Riphaus A. Patient-controlled sedation in endoscopy: are patients leading us? Endoscopy 2013; 45: 920-921
116. Poincloux L, Laquiere A, Bazin JE et al. A randomized controlled trial of endoscopist vs. anaesthetist-administered sedation for colonoscopy. Dig Liver Dis 2011; 43: 553-558
117. Lagasse RS. Anesthesia safety: model or myth? A review of the published literature and analysis of current original data. Anesthesiology 2002; 97: 1609-1617
118. Sieg A, Beck S, Scholl SG et al. Safety analysis of endoscopist-directed propofol sedation: a prospective, national multicenter study of 24 441 patients in German outpatient practices. J Gastroenterol Hepatol 2014; 29: 517-523
119. Simon MA, Bordas JM, Campo R et al. [Consensus document of the Spanish Association of Gastroenterology on sedoanalgesia in digestive endoscopy]. Gastroenterol Hepatol 2006; 29: 131-149
120. Igea F, Casellas JA, Gonzalez-Huix F et al. Sedation for gastrointestinal endoscopy. Clinical practice guidelines of the Sociedad Espanola de Endoscopia Digestiva. Rev Esp Enferm Dig 2014; 106: 195-211
121. Ferlitsch M, Moss A, Hassan C et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2017; 49: 270-297
122. Lin JS, Piper MA, Perdue LA et al. Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama 2016; 315: 2576-2594
123. Pickhardt PJ, Choi JR, Hwang I et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med 2003; 349: 2191-2200
124. Jacob A, Schafer A, Yong J et al. Endocuff Vision-assisted colonoscopy: a randomized controlled trial. ANZ J Surg 2019; 89: E174-e178
125. Williet N, Tournier Q, Vernet C et al. Effect of Endocuff-assisted colonoscopy on adenoma detection rate: meta-analysis of randomized controlled trials. Endoscopy 2018; 50: 846-860
126. Triantafyllou K, Polymeros D, Apostolopoulos P et al. Endocuff-assisted colonoscopy is associated with a lower adenoma miss rate: a multicenter randomized tandem study. Endoscopy 2017; 49: 1051-1060
127. Ngu WS, Bevan R, Tsiamoulos ZP et al. Improved adenoma detection with Endocuff Vision: the ADENOMA randomised controlled trial. Gut 2019; 68: 280-288
128. van Doorn SC, van der Vlugt M, Depla A et al. Adenoma detection with Endocuff colonoscopy versus conventional colonoscopy: a multicentre randomised controlled trial. Gut 2017; 66: 438-445
129. Ponugoti P, Lin J, Odze R et al. Prevalence of sessile serrated adenoma/polyp in hyperplastic-appearing diminutive rectosigmoid polyps. Gastrointest Endosc 2017; 85: 622-627
130. Rivero-Sánchez L, López Vicente J, Hernandez Villalba L et al. Endocuff-assisted colonoscopy for surveillance of serrated polyposis syndrome: a multicenter randomized controlled trial. Endoscopy 2019; 51: 637-645
131. Harris PA, Taylor R, Minor BL et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019; 95: 103208
132. Harris PA, Taylor R, Thielke R et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42: 377-381
133. Ward ST, Mohammed MA, Walt R et al. An analysis of the learning curve to achieve competency at colonoscopy using the JETS database. Gut 2014; 63: 1746-1754
134. [Anonymous]. Update on the paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005; 37: 570-578

135. Hazewinkel Y, de Wijkerslooth TR, Stoop EM et al. Prevalence of serrated polyps and association with synchronous advanced neoplasia in screening colonoscopy. Endoscopy 2014; 46: 219-224
136. Kahi CJ, Hewett DG, Norton DL et al. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. Clin Gastroenterol Hepatol 2011; 9: 42-46
137. Oliveira Ferreira A, Fidalgo C, Palmela C et al. Adenoma Detection Rate: I Will Show You Mine if You Show Me Yours. GE - Portuguese Journal of Gastroenterology 2017; 24: 61-67
138. Floer M, Biecker E, Fitzlaff R et al. Higher adenoma detection rates with endocuff-assisted colonoscopy - a randomized controlled multicenter trial. PLoS One 2014; 9: e114267
139. Bateman AC, Shepherd NA. UK guidance for the pathological reporting of serrated lesions of the colorectum. J Clin Pathol 2015; 68: 585-591
140. Rex DK, Ahnen DJ, Baron JA et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol 2012; 107: 1315-1329; quiz 1314, 1330
141. Pohl H, Robertson DJ. Colorectal cancers detected after colonoscopy frequently result from missed lesions. Clin Gastroenterol Hepatol 2010; 8: 858-864
142. Baek MD, Jackson CS, Lunn J et al. Endocuff assisted colonoscopy significantly increases sessile serrated adenoma detection in veterans. J Gastrointest Oncol 2017; 8: 636-642
143. Triantafyllou K, Gkolfakis P, Tziatzios G et al. Effect of Endocuff use on colonoscopy outcomes: A systematic review and meta-analysis. World J Gastroenterol 2019; 25: 1158-1170
144. Karsenti D, Tharsis G, Perrot B et al. Adenoma detection by Endocuff-assisted versus standard colonoscopy in routine practice: a cluster-randomised crossover trial. Gut 2020, DOI: 10.1136/gutjnl-2019-319565:
145. Edwards BK, Noone AM, Mariotto AB et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer 2014; 120: 1290-1314
146. Ferlay J, Soerjomataram I, Ervik M et al. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. In, GLOBOCAN 2012 v10. Lyon, France: International Agency for Research on Cancer; 2013
147. Vișovan, II, Tanțău M, Pascu O et al. The role of narrow band imaging in colorectal polyp detection. Bosn J Basic Med Sci 2017; 17: 152-158
148. Singh R, Cheong KL, Zorron Cheng Tao Pu L et al. Multicenter randomised controlled trial comparing the high definition white light endoscopy and the bright narrow band imaging for colon polyps. World J Gastrointest Endosc 2017; 9: 273-281
149. Rastogi A, Bansal A, Rao DS et al. Higher adenoma detection rates with cap-assisted colonoscopy: a randomised controlled trial. Gut 2012; 61: 402-408
150. Aziz M, Desai M, Hassan S et al. Improving serrated adenoma detection rate in the colon by electronic chromoendoscopy and distal attachment: systematic review and meta-analysis. Gastrointest Endosc 2019; 90: 721-731.e721
151. Ferreira AO, Costa-Santos MP, Gomes C et al. Participation in clinical trials increases the detection of pre-malignant lesions during colonoscopy. Rev Esp Enferm Dig 2021, DOI: 10.17235/reed.2021.8104/2021:
152. Rex DK, Clodfelter R, Rahmani F et al. Narrow-band imaging versus white light for the detection of proximal colon serrated lesions: a randomized, controlled trial. Gastrointest Endosc 2016; 83: 166-171
153. Alburquerque M, Smarrelli A, Montesinos JC et al. Outcomes of colonoscopy with non-anesthesiologist-administered propofol (NAAP): an equivalence trial. Endosc Int Open 2021; 9: E1070-e1076
154. Dossa F, Medeiros B, Keng C et al. Propofol versus midazolam with or without short-acting opioids for sedation in colonoscopy: a systematic review and meta-analysis of safety, satisfaction, and efficiency outcomes. Gastrointest Endosc 2020; 91: 1015-1026.e1017
155. Wadhwa V, Issa D, Garg S et al. Similar Risk of Cardiopulmonary Adverse Events Between Propofol and Traditional Anesthesia for Gastrointestinal Endoscopy: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2017; 15: 194-206

156. Sulz MC, Kroger A, Prakash M et al. Meta-Analysis of the Effect of Bowel Preparation on Adenoma Detection: Early Adenomas Affected Stronger than Advanced Adenomas. PLoS One 2016; 11: e0154149
157. Radaelli F, Paggi S, Repici A et al. Barriers against split-dose bowel preparation for colonoscopy. Gut 2016, DOI: 10.1136/gutjnl-2015-311049:
158. Kahi CJ, Ballard D, Shah AS et al. Impact of a quarterly report card on colonoscopy quality measures. Gastrointest Endosc 2013; 77: 925-931
159. Hassan C, Spadaccini M, Iannone A et al. Performance of artificial intelligence in colonoscopy for adenoma and polyp detection: a systematic review and meta-analysis. Gastrointest Endosc 2021; 93: 77-85.e76