75013_Auto_Edited-check.docx

WORD COUNT	3674	TIME SUBMITTED	04-JUL-2022 03:08PM
		PAPER ID	87990636

Name of Journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 75013

Manuscript Type: ORIGINAL ARTICLE

Observational Study

To scope of not - the challenges of managing patients with positive fecal occult blood test after recent colonoscopy

Abstract

BACKGROUND

Colorectal cancer (CRC) is a major health problem. There is minimal consensus of the appropriate approach to manage patients with positive immunochemical fecal occult blood test (iFOBT), following a recent colonoscopy.

AIM

To determine the prevalence of advanced neoplasia in patients with a positive iFOBT after a recent colonoscopy, and clinical and endoscopic predictors for advanced neoplasia.

METHODS

The study recruited iFOBT positive patients who underwent colonoscopy between July 2015 to March 2020. Data collected included demographics, clinical characteristics, previous and current colonoscopy findings. Primary outcome was the prevalence of CRC and advanced neoplasia in a patient with positive iFOBT and previous colonoscopy. Secondary outcomes included identifying any clinical and endoscopic predictors for advanced neoplasia.

RESULTS

The study included 1051 patients (male 53.6%; median age 63). Forty-two (4.0%) patients were diagnosed with CRC, 513 (48.8%) with adenoma/sessile serrated lesion (A-SSL) and 257 (24.5%) with advanced A-SSL (AA-SSL). A previous colonoscopy had been performed in 319 (30.3%). In this cohort, four (1.3%) were diagnosed with CRC, 146 (45.8%) with A-SSL and 56 (17.6%) with AA-SSL. Among those who had a colonoscopy within 4 years, none had CRC and 7 had AA-SSL. Of the 732 patients with no prior colonoscopy, there were 38 CRCs (5.2%). Independent predictors for advanced neoplasia were male [odds ratio (OR) = 1.80; 95% confidence interval (CI): 1.35-2.40; P <

0.001), age (OR = 1.04; 95%CI: 1.02-1.06; $P < 0.001$) and no previous colonoscopy (OR = 2.07; 95%CI: 1.49-2.87; $P < 0.001$).

CONCLUSION

A previous colonoscopy, irrespective of its result, was associated with low prevalence of advanced neoplasia, and if performed within four years of a positive iFOBT result, was protective against CRC.

Key Words: Colorectal cancer; Adenoma; Screening; Fecal occult blood test; Colonoscopy

Rattan N, Willmann L, Aston D, George S, Bassan M, Abi-Hanna D, Anandabaskaran S, Ermerak G, Ng W, Koo JH. To scope of not - the challenges of managing patients with positive fecal occult blood test after recent colonoscopy. *World J Gastrointest Oncol* 2022; In press

Core Tip: Currently, there is minimal consensus to inform clinicians of the appropriate approach to manage patients presenting with positive immunochemical fecal occult blood test (iFOBT) following a recent colonoscopy. This may lead to additional unnecessary, invasive procedure which confers procedure-related risks, as well as avoidable patient anxiety and a higher cost-burden on the healthcare system. Our study revealed that a previous colonoscopy, irrespective of its result, was associated with low prevalence of advanced neoplasia, and if performed within 4 years of a positive iFOBT result, was protective against colorectal cancer.

INTRODUCTION

Colorectal cancer (CRC) is the fourth most-commonly diagnosed malignancy and second-highest cause of cancer mortality in Australia[1]. Screening for CRC with a fecal occult blood (FOBT) test is essential in early detection and management, leading to

reduction in CRC-related mortality[2,3]. When diagnosed early, CRC has excellent prognosis, with a 5-year survival rate of up to 93%[4,5]. In Australia, the National Bowel Cancer Screening Program (NBCSP) invites those 50 to 74 years of age to participate in biennial immunochemical FOBT (iFOBT) screening. Of those undergoing colonoscopy, 1 in 41 had a CRC diagnosis, resulting in a 15% reduction in mortality in the screened population when compared with non-screened population[1,4]. The NBCSP automatically invites subjects to participate in screening at the designated ages, irrespective of having had a previous colonoscopy. In individuals who have had a recent colonoscopy, this may lead to an unnecessary, invasive procedure which confers procedure-related risks, as well as avoidable patient anxiety and a higher cost-burden on the healthcare system[6,7]. Despite aiming to shift resources from surveillance to screening, this may paradoxically place greater burden on the need for repeat procedures, and potentially drain resources. Hence, there is a need to optimize the utilization of available resources, specifically to determine the widest acceptable surveillance interval in those with a prior colonoscopy that still confers a reduction in CRC mortality. Currently, there is limited data and minimal consensus to inform clinicians of the appropriate approach to manage patients presenting with positive iFOBT following a recent colonoscopy. The primary aim of this study was to determine the prevalence of advanced neoplasia, defined as CRC and advanced adenoma or sessile serrated lesions, in a patient presenting with positive iFOBT, after having had a previous colonoscopy. The secondary aim was to determine any clinical, biochemical, and endoscopic predictors of advanced neoplasia in these patients.

MATERIALS AND METHODS

Study design

This cohort study included iFOBT-positive patients between the ages of 50 and 75 years who were referred for a colonoscopy at a high-volume Australian tertiary referral center between July 2015 to March 2020. A positive iFOBT result was determined during population-based or opportunistic screening.

Data collection and statistical analysis

Data was prospectively collected from patients including demographics such as age, gender, family history of CRC, aspirin use, diabetes and gastrointestinal symptoms (rectal bleeding, altered bowel habits, abdominal pain, unexplained weight loss and anemia). Prior and current colonoscopy timing and findings were retrieved from the centre's electronic medical records and treating proceduralists' records. Data obtained included quality of bowel preparation, completion to cecum or terminal ileum, pathology identified and histopathology. Only completed colonoscopies were included for patients who required a repeat procedure if the initial colonoscopy was unable to be completed due to poor quality of bowel preparation. All colonoscopies were performed by 12 experienced gastroenterologists. Statistical analysis was performed using IBM SPSS statistics (version 22; IBM Corp., Armonk, NY, United States) including χ^2 test for categorical variables, the Mann-Whitney U test to assess differences between non-parametric continuous variables and binary logistic regression to assess for predictors of advanced neoplasia and CRC.

Definitions

Polyps were classified as adenomas/sessile serrated lesions (A-SSL), or non-adenomas based on histopathology. An advanced A-SSL (AA-SSL) was defined as an adenoma measuring ≥ 10mm in diameter, having high-grade dysplasia or villous or tubulovillous architecture or a sessile serrated lesion measuring ≥ 10mm in diameter with or without dysplasia. Advanced neoplasia was defined as an AA-SSL, carcinoma *in situ* or invasive CRC. A colonoscopy was deemed complete if the endoscope was advanced to the cecum or terminal ileum.

Ethics

The local institution's Human Research and Ethics Committee approved the study (HREC/LNR/15/LPOOL/186).

RESULTS

Patient demographics

The study involved data collected from 1051 iFOBT-positive patients (male 563, 53.6%; median age 63, range 50 to 75 years) from July 2015 to March 2020. Within this group, 108 patients (10.3%) had a family history of CRC with this being a first degree relative in 78 (father 31, mother 22, sibling 25). A total of 407 patients (38.7%) were symptomatic at the time of presentation, with symptoms including rectal bleeding (n = 178; 16.9%), altered bowel habits (n = 181, 17.2%), abdominal pain (n = 81, 7.7%), unintentional weight loss (n = 53, 5.0%) and anemia (n = 59, 5.6%). Just over thirty percent of patients had a previous colonoscopy (n = 319), and 47 patients (4.5%) could not recall having undergone a colonoscopy.

Current colonoscopy findings

The bowel preparation was reported as excellent or good in 736 (70%), fair/adequate/satisfactory in 246 (23.4%) and poor in 69 (6.6%) patients. Complete colonoscopy was achieved in 1026 (97.6%) patients. Overall, 42 (4.0%) patients were diagnosed with CRC. The A-SSL detection rate was 48.8% (n = 513) while 54 (5.1%) patients had non-adenomatous polyps and 466 (44.3%) patients had no polyps. There were 257 (24.5%) patients with AA-SSL and cumulatively 281 (26.7%) with advanced neoplasia detected. The number of polyps detected ranged from 1 to 13 (mean 2.26 ± 1.69, median 2.0). The size of the polyps ranged from 1 to 65mm (mean 9.24 ± 6.50 mm, median 8.0mm). Other pathology identified at colonoscopy included diverticulosis (n = 240, 22.8%), hemorrhoids (n = 215, 20.4%), colonic angioectasia (n = 14, 1.3%) and inflammatory bowel disease (n = 2), while 121 (11.5%) patients had a normal colonoscopy. Demographics and colonoscopy outcomes in patients with and without a previous colonoscopy are described in Table 1.

Previous colonoscopy findings

For most patients who had a previous colonoscopy, it was performed more than 5 years earlier (63.9%). The time of previous colonoscopy in relation to current procedure is depicted in Table 2. With respect to previous colonoscopies, the quality of bowel preparation was reported as excellent or good in 66 patients, fair/satisfactory/adequate in 28, poor in 21 and unknown in 204 (63.9%) patients. The colonoscopy was complete in 106 (33.2%) cases, incomplete in eight patients and the extent of insertion was unknown for 205 (64.2%) patients. In 84 (26.3%) patients, the previous colonoscopy findings were unable to be obtained. Where results were available, colonoscopy findings included one CRC and 95 patients had at least one polyp detected (25 patients had adenomas, and the remaining were non-adenomatous polyps). Other findings included diverticulosis (n = 19) and hemorrhoids (n = 20). There were 100 patients who had a previous normal colonoscopy.

Current colonoscopy findings in the context of previous colonoscopy

Of the 319 patients who had a previous colonoscopy, four (1.3%) were diagnosed with CRC and 56 (17.6%) had AA-SSL on their current colonoscopies. Of the four CRC cases, one patient was diagnosed 4 years and 7 mo after a normal index colonoscopy, where the bowel preparation was reported as good. Another patient had a prior colonoscopy 7 years earlier and was symptomatic with abdominal pain prior to the current procedure. The remaining two patients diagnosed with CRC had a prior colonoscopy greater than 10 years ago, and their prior colonoscopy findings including bowel preparation were unavailable. Details of these four patients' previous and current colonoscopy findings and American Joint Committee on Cancer (AJCC) staging of CRC at diagnosis are summarised[8] in Table 3.

Among the 732 patients who had no prior colonoscopy or were uncertain about a previous procedure, 38 (5.2%) and 200 (27.3%) patients were diagnosed with CRC and AA-SSL respectively, and these were significantly higher than those who had an index colonoscopy. Also, these patients were younger, had fewer family members with CRC and were more likely to be asymptomatic at the time of their current colonoscopy (Table

1). The prevalence of AA-SSL, advanced neoplasia, and CRC on the current colonoscopy according to the time since the previous colonoscopy, are presented in Table 4. Among patients who had their index colonoscopy within 4 years (n = 68), there was no CRC detected on their current colonoscopy, while 7 patients had an AA-SSL detected. Details of these seven patients' previous and current colonoscopy findings are summarised in Table 5.

Predictors of advanced neoplasia

In multi-variate analysis using binary logistic regression of the entire cohort, male gender, age, and no previous colonoscopy were independent predictors of advanced neoplasia. The univariate and multivariate predictors of advanced neoplasia of the entire cohort are reported in Table 6. In the cohort with a previous colonoscopy, univariate analysis using binary logistic regression identified age over 65 years [odds ratio (OR) = 1.94; 95% confidence interval (CI): 1.08-3.46; P = 0.03) as the only predictor of advanced neoplasia. Male gender, family history of CRC, symptoms, quality of bowel preparation and completion of the index colonoscopy were not statistically significant. Due to the small number of CRC diagnosis in this cohort, we were unable to analyze the clinical predictors of CRC detection.

DISCUSSION

In Australia, nationwide biennial iFOBT invitations have resulted in a significant influx in patients presenting for colonoscopy, thus anticipating a sustained increase over time. Strategies to avoid unnecessary procedures would help distribute resources more effectively, leading to improved management of waitlists, reducing patient anxiety and the cost-burden on the healthcare system[6,7]. While a colonoscopy is recommended in a patient with a positive iFOBT, the decision to proceed in those with a previous colonoscopy is often unclear and guidelines are lacking. The concern exists for interval pathology, especially CRC, likely influenced by the timing between procedures and quality of the preceding colonoscopy. Colonoscopy is not a perfect procedure and rates

of missed lesions are well documented, with the quality of colonoscopy dependent on multiple factors including the proceduralist's adenoma detection rate, withdrawal times and quality of bowel preparation[9,10]. However, avoiding an unnecessary colonoscopy would be ideal if one can be confident that the preceding colonoscopy did not miss advanced colorectal pathology.

Our study aimed to determine the widest acceptable interval between consecutive colonoscopies that maintains patient safety through a reduction in CRC incidence whilst optimising healthcare resource utilisation. We found that despite presenting with a positive iFOBT, there was no CRC detected among the 68 patients with an index colonoscopy within 4 years of their current procedure, irrespective of the results of their index procedures. Of these patients, 7 had an AA-SSL detected, although four were classified based on size greater than 10 mm alone, without having other high-risk features such as villous architecture or high-grade dysplasia. Excluding these patients, the rate of AA-SSL detection was 4.4%. In three patients with AA-SSL, the bowel preparation of the index procedure was suboptimal, thereby increasing the possibility of missed lesions. Two patients were symptomatic at the time of their current examination, and none had a family history of CRC. Our study found that having a previous colonoscopy for any clinical indication was associated with a lower risk of advanced neoplasia in subsequent testing. A similar protective effect of a prior colonoscopy has been reported by another study, with a risk reduction of CRC of 67%-85% for up to 10 years[11].

Several studies have supported deferring a colonoscopy after a positive FOBT in patients who have had a previous procedure. A prospective study of asymptomatic, average-risk, predominantly male Veteran Affairs healthcare population reported an advanced adenoma detection rate of 1.1% and no CRC cases in positive guaiac-FOBT patients following a normal colonoscopy within 5 years[12]. The study recommended a cut-off interval of 5 years for an asymptomatic average-risk screening population after a recent normal colonoscopy. Compared with our study, the prevalence of advanced adenoma was considerably lower in this cohort, as it only included an asymptomatic,

average-risk patient population who had a previously normal colonoscopy. Our study also utilised iFOBT, which has greater sensitivity for detecting occult colonic bleeding, as compared with guaiac-FOBT.

Similarly, another study compared the prevalence of CRC and advanced neoplasia following positive iFOBT in average-risk, asymptomatic patients with or without an index colonoscopy, categorised according to specific time frames following their previous procedure[13]. The prevalence of CRC in those without a previous colonoscopy, with a colonoscopy within 5 years and greater than 5 years were comparable with our study (5.7%, 0.3% and 1.2% respectively, compared with our study of 5.4%, 0.9% and 1.4%). After stratifying their results according to the severity of adenomas in the previous colonoscopy, the prevalence of advanced neoplasia was only 2.9% among patients who had low-risk adenomas detected within 5 years. They concluded that a colonoscopy should not be recommended within 5 years of a prior colonoscopy in average-risk patients with previous low-risk adenomas.

However, several studies have reported conflicting outcomes. Kim *et al*[14] reported 16 (2.1%) iFOBT positive patients were diagnosed with CRC after having an index colonoscopy within 3 years. Carrera *et al*[15] reported 3.8% of 157 guaiac-FOBT positive patients were diagnosed with CRC in second-round biennial screening after a negative colonoscopy. Similarly, a study revealed CRC was diagnosed in 0.4% (3 of 740) patients with positive guaiac-FOBT within 28 mo after their index negative colonoscopy[16]. A recent study by Peng *et al*[17] reported that the incidence of CRC following a negative colonoscopy was significantly lower in patients who recommenced iFOBT as compared to those who did not (incidence: 1.34 *vs* 2.69 per 1000 person years; adjusted OR = 0.47). Notably, of those who undertook iFOBT screening, the incidence of CRC was highest in those who had their subsequent iFOBT between 1.5 to 3 years, as compared to those performed 5 years or more (1.46 *vs* 1.08 per 1000 person years). While these studies demonstrated a benefit from undergoing colonoscopy within 3 years of the index procedure when presenting with a positive FOBT, the results are difficult to interpret as quality indicators of the index colonoscopy were not reported and these are key

predictors of missed lesions[14-17]. The colonoscopies done at such short intervals were principally to detect missed or rapidly evolving lesions to compensate for the compromised effectiveness of a potentially inadequate quality index colonoscopy.

The latest consensus by the US Multi-Society Task Force on Colorectal Cancer is to offer colonoscopy following positive FOBT even if colonoscopy was performed recently; however, the recommendation was considered weak and the available quality of evidence low[6]. It recommended that the clinician considers the clinical context, such as presence or absence of symptoms of CRC, CRC risk factors such as family history, the quality and results of the index colonoscopy including the adequacy of bowel preparation, completion of procedure to the cecum and the proceduralist's adenoma detection and cecal intubation rates, and then balances this with the procedural risks of having another colonoscopy within a short time frame.

Strengths and limitations

A high-quality colonoscopy is paramount in reducing the likelihood of missed lesions and interval CRC. A limitation of our study is that quality indicators of the previous colonoscopy such as the proceduralists' adenoma detection rate and assessment of bowel preparation were not available, thus may have impacted upon our findings and the likelihood of detecting advanced neoplasia on their current procedures. We were unable to retrieve a proportion of patients' index colonoscopy reports and hence could not make any conclusions on the important association of advanced lesions at the index colonoscopy with the current colonoscopy. Furthermore, due to the small number of CRC cases in patients with a prior colonoscopy, we were unable to report on the clinical predictors of CRC detection in this cohort. Additional studies assessing quality indicators and presence of advanced lesions of the index colonoscopy should be performed to determine predictors of interval lesions in patients with positive iFOBT following previous colonoscopy. Our study did not include patients who had a normal index colonoscopy but were subsequently diagnosed with interval CRC without iFOBT being performed. Further studies evaluating all CRCs diagnosed and reviewing

colonoscopy findings and FOBT screening history may be worthwhile. Data on previous colonoscopy was obtained retrospectively, and patient recall was relied upon where procedure or histopathology reports were inaccessible, which may be subject to recall bias. In our study, two of the four patients with CRC detected on current colonoscopy recalled their prior procedures as more than 10 years earlier but the specific time interval was unable to be confirmed with procedure reports. Nevertheless, despite these limitations, this study represents a large cohort of patients in a "real-world" scenario, where healthcare provision is often fragmented, screening programs are centrally driven, and primary care physicians are not always involved with delivering or coordinating screening programs for their patients. Therefore, our study results are applicable within similar clinical settings, as our population of patients are of varying demographics and heterogenous risk profiles, therefore reflecting real-life clinical practice and improving the overall reproducibility of the study. Furthermore, the overall A-SSL detection rates, cecal intubation rates and bowel preparation quality exceeded the recommended level, further supporting the validity of this cohort as representative of a real-life population[8].

CONCLUSION

The decision to perform a colonoscopy following a positive iFOBT in a patient with a recent colonoscopy remains a challenging one. In our study, a previous colonoscopy, irrespective of its indication or findings, was associated with low prevalence of advanced neoplasia, and was protective against the detection of CRC if performed within 4 years of the positive iFOBT result. Our study suggests that a colonoscopy could be deferred following a positive iFOBT result for patients with a high-quality colonoscopy performed within 4 years. However, a colonoscopy should be repeated if there are concerns about the quality of the prior colonoscopy or presence of high-risk clinical features.

ARTICLE HIGHLIGHTS

Research background

There is currently minimal consensus to inform clinicians of the best approach to manage patients presenting with positive immunochemical fecal occult blood test (iFOBT) after having a recent colonoscopy. Repeating the colonoscopy within a short time frame may expose to the patient to unnecessary procedure-related risks, avoidable patient anxiety and a higher cost-burden on the healthcare system.

Research motivation

The primary motivation for this study was to determine the widest acceptable interval between consecutive colonoscopies that maintains patient safety through a reduction in CRC incidence whilst optimizing healthcare resource utilization.

Research objectives

To determine the prevalence of colorectal cancer (CRC) and advanced neoplasia in patients with a positive iFOBT after a recent colonoscopy, and clinical and endoscopic predictors for advanced neoplasia.

Research methods

This study included iFOBT-positive patients who were referred for a colonoscopy at a high-volume Australian tertiary referral center. Data was prospectively collected including demographics, quality indicators and results of current and previous colonoscopy. The main outcome was to determine the prevalence of CRC and advanced neoplasia in a patient with positive iFOBT who had a previous colonoscopy.

Research results

Of the 1051 patients included in the study, 319 (30.3%) had a previous colonoscopy. In this group, four patients were diagnosed with CRC. Among those who had a colonoscopy within four years, none were diagnosed with CRC and 7 had advanced

adenomas/sessile serrated lesions. Of the 732 patients with no prior colonoscopy, there were 38 CRC (5.2%).

Research conclusions

Our study revealed that a previous colonoscopy, irrespective of its result, was associated with low prevalence of advanced neoplasia, and if performed within 4 years of a positive iFOBT result, was protective against CRC.

Research perspectives

Our study suggests that a colonoscopy could be deferred following a positive iFOBT result for patients who had a high-quality colonoscopy performed within 4 years. However, a colonoscopy should be repeated if there are concerns about the quality of the prior colonoscopy or presence of high-risk clinical features.

75013_Auto_Edited-check.docx

ORIGINALITY REPORT

3%
SIMILARITY INDEX

PRIMARY SOURCES

1	Nivedita Rattan, Sulak Anandabaskaran, Diana Aston, George G. Ermerak, Watson Ng, Milan S. Bassan, David Abi-Hanna, Jenn H. Koo. "Su1659 – Positive Faecal Occult Blood Test After a Previous Negative Colonoscopy - to Scope Or Not?", Gastroenterology, 2019 Crossref	44 words — 1%
2	Nam Hee Kim, Yoon Suk Jung, Jae Wan Lim, Jung Ho Park, Dong Il Park, Chong Il Sohn. "Yield of repeat colonoscopy in asymptomatic individuals with a positive fecal immunochemical test and recent colonoscopy", Gastrointestinal Endoscopy, 2019 Crossref	29 words — 1%
3	www.frontiersin.org Internet	17 words — < 1%
4	www.dovepress.com Internet	15 words — < 1%
5	"Scientific Abstracts", Reproductive Sciences, 2012 Crossref	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS