Surveillance colonoscopy for Lynch syndrome in the Northern Cape:

Does direct contact improve compliance?

by

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Abstract

Introduction

The Annual Northern Cape Colonoscopy Outreach program provides surveillance colonoscopy to high–risk individuals known with Lynch syndrome along the west coast and in the Northern Cape Province of South Africa. There are currently over 100 known mutation positive individuals. Surveillance colonoscopies are performed annually in August/September, and are preceded a by a preparation visit approximately 6-8 weeks prior. The aim of the preparation trip has been to directly impart information, regarding preparation and importance of attendance, to individuals required to attend annual surveillance. During the preparation trip an attempt is made to reach all individuals scheduled for surveillance but due to the vastness of the Northern Cape inevitably every year some areas are not visited. It has been noted that over the past few years fewer than 25 % of the total participants obtained 100 % adherence to surveillance.[1]

Objectives

The primary objective of this study is to determine whether there is a need for a yearly colonoscopy preparation visit to high–risk individuals in the Northern Cape. The study determines if direct interaction with patients prior to surveillance colonoscopy will significantly impact attendance and adequacy of bowel preparation.

Methods

Seventy-eight individuals known with a genetic mutation for Lynch syndrome were enrolled in this randomised crossover trial spanning two years of surveillance. In 2014 the control group of individuals had bowel preparation and instructions forwarded to their local clinics and distributed to them via clinic or hospital staff. The intervention group of individuals were personally visited and provided with instructions and bowel preparation by the research team. In 2015 there was a crossover of the control and test groups. A measurement of attendance at surveillance colonoscopy as well as

cleanliness of the colon was recorded for each year of study.

Results

The study cohort consisted of 28 (36%) male and 50 (64%) female participants with a median age of 39.5 years. Groups A and B consisted of 38 and 40 participants respectively. In September 2014 thirty-six (46.2%) participants presented for annual surveillance colonoscopy, 19 (50%) from the control group and 17 (42.5%) from the intervention group. In 2015 there were 41 (53%) compliant individuals; this included 21 (55%) individuals receiving a preparatory direct contact visit, and 20 (50%) individuals from the 2015 control group. Following exclusion of carry-over and period effect, the study intervention was found not to significantly impact attendance ($P = 0.853$). Superior attendance was noted in individuals with prior compliance to surveillance ($P = 0.001$).

Conclusions

Direct interaction with known Lynch syndrome individuals prior to annual surveillance colonoscopy has not shown to positively impact attendance. Interaction and counselling should focus on individuals identified to be defaulting surveillance.

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To my academic advisor, Professor Paul Goldberg, thank you. During the duration of my dissertation, he contributed to a rewarding research experience by giving me intellectual independence in my work. He has allowed me to engage in new experiences, learning to master excellence in all my endeavours.

A special thanks to Sister Ursula Algar, co-ordinator of the Annual Northern Cape Colonoscopy Outreach program, she is an unfaltering friend and mentor. Her commitment to her patients and willingness to assist in any way possible is an inspiration.

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Abbreviations

APC	adenomatous polyposis coli
BRAF	B-raf proto-oncogene
CDC4	cell division control protein 4
CI	confidence interval
CIMP	CpG island hypermethylation phenotype
CIN	chromosomal instability
CRC	colorectal cancer
CpG	5'—C—phosphate—G—3' sequence
DNA	deoxyribonucleic acid
EGAPP	Evaluation of Genomic Application in Practice and Prevention
EPCAM	epithelial cell adhesion molecule
FAP	familial adenomatous polyposis
fCRCtX	familial colorectal cancer type X
FOBT	faecal occult blood test
HNPCC	hereditary non-polyposis colorectal cancer
IGF2R	insulin-like growth factor 2 receptor
IHC	immunohistochemistry
KRAS	K-ras proto-oncogene
LS	Lynch syndrome
MAP	MUTYH-associated polyposis
MeSH	Medical Subject Headings
MLH1	mutL homolog 1
MMR	mismatch repair

MSI	microsatellite instability
MSI-H	high frequency microsatellite instability
MSH2	mutS homolog 2
MSH6	mutS homolog 6
p53	tumour suppressor p53
PCR	polymerase chain reaction
PMS2	postmeiotic segregation 2
PTEN	phosphatase and tensin homolog
OR	odds ratio
SA	South Africa
Std.dev.	Standard deviation
TGFut	transforming growth factor-lo
TGFBR2	transforming growth factor- β receptor 2
TP53	tumour protein 53
US	United States
WC	Western Cape
Wnt	wingless-related integration site

Chapter 1 – Literature review

1.1 Introduction

Lynch Syndrome and the association with colorectal, and other cancers, is briefly described. The genetics, incidence and global impact of LS are reviewed. Current data with regards to screening, surveillance and adherence to colonoscopy are appraised and the influence of interactive communication is evaluated.

1.2 Search methods

A literature search of relevant literature was performed initially in April 2014 and repeated for new references in April 2015 and February 2017. The literature search was conducted using PubMed (MEDLINE), PubMed Central and the Medical Subject Headings (MeSH) databases. The following search term categories were used in combination: “Lynch syndrome”, ”HNPCC”, “South Africa”, “surveillance colonoscopy”, “screening colonoscopy”, “adherence”, “uptake”, “compliance” and “communication”. The search terms were used for title, abstract, keywords and full text fields. All result types were included. Further sources were identified by following up internal citations and references within the documents retrieved in the initial search. Some South African sourced articles were obtained directly from the author. This review excludes studies that have not been published in English and research currently underway.

1.3 Colon cancer

1.3.1 Classification

The manner in which colorectal cancer originates and is expressed can distinguish three forms: sporadic, familial and hereditary. The sporadic form of tumours appears in individuals carrying no mutation making them susceptible to developing colorectal cancer. This is by far the most common form of CRC (between 60 and 80%).[2] CRC is most common over the age of 50 and has been etiologically associated with dietary and environmental factors.

Familial colorectal cancer type X (fCRCtX), which has no associated identifiable gene, constitutes 20–40% of cases. Population studies show that there is a greater risk, two to three times higher than in the normal population, of developing this tumour when family members of primary consanguinity have suffered from sporadic colon cancer.[3]

Hereditary CRC has two tumour variants that can be distinguished by the predisposition to the development and presence of adenomatous polyps or not. The diseases with polypoid features include familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), and the hamartomatous polyposis syndromes (Peutz-Jeghers, juvenile polyposis, phosphatase and tensin homolog (PTEN) hamartoma tumour syndrome – Cowden syndrome). HNPCC, or Lynch syndrome when there is a known causative mutation, is classified as a non-polypoid tumour variant.

1.3.2 Genetics

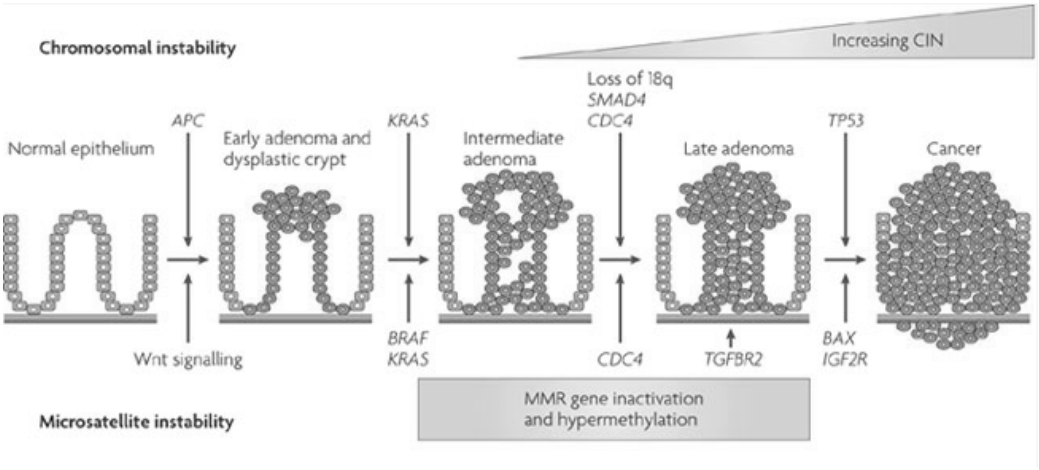
Colon cancer is the result of an accumulation of genetic alterations that drive the transformation of a normal cell to a malignant cell. The development of CRC is influenced by both genetic and environmental factors. The genetic factors influencing the progression to CRC can be sporadic or, as in Lynch syndrome, inherited. A fairly limited number of oncogenes and tumour-suppressor genes are mutated in a considerable fraction of CRCs, most significantly the adenomatous polyposis coli (APC), KRAS, and p53 genes. A greater group of genes that are mutated in subsets of CRC have begun to be defined. In association with DNA-methylation and chromatin-structure changes, the mutations act to dysregulate conserved signalling networks that exert context-dependent effects on critical cell phenotypes. These mutations ultimately impact on the regulation of cellular metabolism, proliferation, differentiation, and survival.[4]

Molecular studies of CRC have revealed that several signalling pathways are involved in its development. These pathways lead to the morphological heterogeneity of CRC, in terms of site, grade and type of the tumour. Three main pathway concepts have now been developed. The first clarified is the classical pathway, of which chromosomal

instability (CIN) is a hallmark. CIN is involved in roughly 80% of colorectal carcinomas. Most of these are due to loss of function mutations of the APC gene (responsible for familial adenomatous polyposis (FAP)). APC mutations also occur in sporadic CRC these however are not germline but somatic.[5] Additional molecular events are activating mutations of KRAS and BRAF proto-oncogenes. The progression of an adenomatous polyp into a malignant carcinoma is now known as the adenoma-carcinoma sequence (Fig. 1).[6] Vogelstein supplemented this concept with molecular data.[7]

The microsatellite instability (MSI) pathway is responsible for the development of hypermutating carcinomas in which the adenoma-carcinoma sequence occurs precipitously. The prototype of these pathways was discovered in the early 1990s while searching for the molecular genetic origins of HNPCC.[8]

Fig. 1: Adenoma–carcinoma sequence model in colorectal cancer[6]



In 1994 it was discovered that Lynch syndrome is caused by a mutation in one of the genes encoding the proteins involved in DNA mismatch repair.[9] MMR corrects routine errors such as single base mismatches or deletions and short insertions occurring during DNA replication. The proteins involved in MMR form a protein complex, this complex binds the mismatch and uses the information from the (correct) complementary strand to excise the error and repair it. When MMR does not function, the cells accumulate errors, which occur also in microsatellite sequences. Mismatch

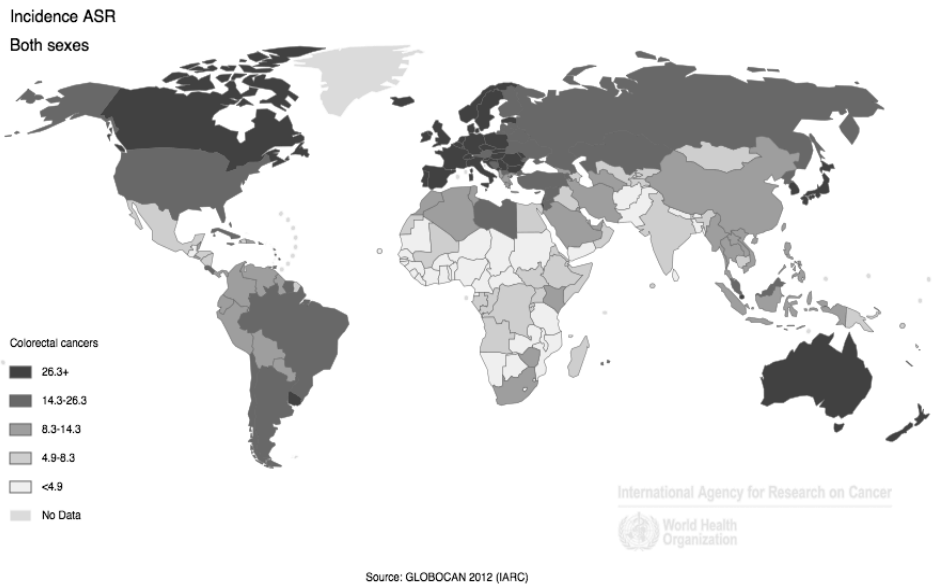
repair proteins (MLH1, MSH2, MSH6 and PMS2) are easily detectable by immunohistochemistry in routinely processed tissue sections and are used as screening for Lynch syndrome.[10] Lynch syndrome is responsible for about 3% of CRC, but MSI occurs in around 12% of sporadic tumours in the colon.[5]

The CpG island hypermethylation phenotype (CIMP) pathway is a mechanism responsible for silencing of tumour suppressor genes and is involved in the regulation of transcription. The molecular events in the pathway include CIMP mutation of the BRAF gene. Carcinomas with CIMP were noted to be associated with serrated precursor lesions. Current evidence suggests that the risk of carcinoma evolution via CIMP is lower than the risk of progression of traditional adenomas.[11]

1.3.3 Incidence

Colorectal cancer is the third most common cancer in men (10% of cancers) and the second in women (9.2% of cancers) worldwide (Fig. 2). Africa demonstrates the lowest rates of CRC, approximately 16 000 new cases annually in men and 15 000 in women.

Fig. 2: Estimated global age-standardised incidence rates per 100,000[12]



The most recent formal statistics available for CRC in South Africa, according to the National Cancer Registry, were histologically diagnosed during 2010 (table 1).[13] In the Northern Cape the annual incidence of CRC was 3.7/100 000 population (3.5/100 000 for men and 3.9/100 000 for women).[14]

Table 1: Incidence and risk of colorectal cancer in South Africa[13]

2010	No of cases		Lifetime risk		Percentage of all cancers	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**
Total	1295	1132	1:114	1:182	4.77%	3.80%
Asian	100	71	1:51	1:97	13.62%	7.39%
Black	407	397	1:264	1:389	3.84%	2.54%
Coloured	180	144	1:79	1:103	5.64%	4.66%
White	608	520	1:50	1:71	4.83%	5.17%

1.4 Lynch syndrome

Lynch syndrome is a hereditary syndrome of the HNPCC variant. It carries a genetic predisposition to CRC, as well as extracolonic malignancies, and is the most common cause of hereditary colon cancers. The syndrome was first described in 1913 by Alfred Warthin and further characterised by Henry Lynch in 1974.[15] In 1984 Boland and Troncale coined the term Lynch syndrome to refer to this disorder.[16] Hereditary non-polyposis colorectal cancer is now termed Lynch syndrome when there is a known causative genetic mutation.

1.4.1 Genetics

Lynch syndrome is inherited in an autosomal dominant manner, and equally affects male and female family members. By designation, LS is associated with DNA mismatch repair gene mutations. There are four MMR genes that are linked to LS,

MutL homolog 1 (MLH1), MutS homolog 2 (MSH2), MutS homolog 6 (MSH6) and postmeiotic segregation 2 (PMS2). Among individuals with identifiable germline mutations in the MMR genes, mutations in MLH1, MSH2, MSH6, and PMS2 are found in approximately 32, 39, 15, and 14 %, respectively.[17] In addition, deletions of the terminal codon of the epithelial cell adhesion molecule (EPCAM) gene, located alongside the MSH2 gene, result in silencing of the MSH2 gene in tissues that express EPCAM. This deletion produces a phenotype very similar to LS.

As previously described, the inactivation of these MMR genes causes an alteration in the repetitive sequences or microsatellites (the MSI pathway) leading to a prompter progression of the adenoma-carcinoma sequence. The adenoma-carcinoma sequence in LS is estimated at 35 months compared with 10-15 years in sporadic cancer.[18]

CRC develops earlier in patients with a known germline mutation in one allele of a MMR gene, and the second allele (inherited from unaffected parent) is somatically inactivated by either somatic mutation, loss of heterozygosity, or epigenetic silencing by promoter hypermethylation. Thus, the tumours occur after somatic biallelic gene inactivation, with one mutation inherited and the other acquired.

1.4.2 Incidence

The incidence Lynch syndrome is approximately 2-3%.[19,20] In the United States the population incidence of LS, based on the 2.8% incidence of LS among newly diagnosed CRC, is approximately 1 in 370.[19]

Carriers of an MMR gene mutation have a very high risk of developing CRC. Most reports of lifetime risks of CRC for MLH1 and MSH2 gene mutation carriers range from 35 to 70%.[20–23] The lifetime risk of CRC in LS appears to be dependent on gender and the MMR gene mutated.

Patients with a known gremline MMR mutation are at increased risk for extracolonic neoplasms. The most common extracolonic tumour in Lynch syndrome is endometrial cancer. The risk of endometrial cancer varies depending on the MMR mutation. Following CRC, MMR mutation carriers showed a 12% (95% CI = 8-17%) 10-year risk for endometrial cancer.[24] In another series the estimated ten-year cumulative risk of endometrial cancer subsequent to CRC was 23.4% (95% CI = 15–36%) for Lynch

syndrome women.[25] The lifetime risk of cancers has been shown to vary according to the carriers Lynch genotype. (table 2)

Lynch syndrome ‐ related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract and brain tumours, sebaceous gland adenomas and keratoacanthomas, and carcinoma of the small bowel.

Table 2: Lifetime cancer risk relative to MMR genotype[19–24,26,27]

Cancer site	MLH1	MSH2	MSH6	PMS2
Any Lynch cancer	44-79%	38-78%	25-65%	16-53%
Colorectal	50-65%	35-70%	18-69%	15-20%
Endometrial	57-66%	21%	12-44%	15%
Ovarian	20%	24%	1%	
Upper Urological	0.4-2.1%	9-20%	0.7%	
Gastric	6%	2%	4-6%	
Small bowel	3-6%	3-6%		
Biliary/ Pancreatic	4%			
Brain (gliomas)	1.7%	2.5%		

In the Northern Cape Province of South Africa, an area with a low incidence of colorectal cancer (3.7/100 000)[14], 10.5% of colorectal cancers were found to have MMR mutation on immunohistochemical testing.[28] This was noted to be approximately three times the reported rate in high-incidence areas.

1.5 Screening for Lynch syndrome

1.5.1 Risk assessment

A detailed family history can assist in identifying families who should be referred for further testing to diagnose or exclude Lynch syndrome. In 1989, the Amsterdam criteria (table 3) were proposed in order to provide reliable family material required for international collaborative studies. Revision of these criteria in 1999 included various extracolonic tumours. The sensitivity and specificity of Amsterdam II criteria for a diagnosis of Lynch syndrome are 22 and 98 %, respectively.[29]

Table 3: Amsterdam II criteria for gene testing for Lynch syndrome

There should be at least three relatives with colorectal cancer (CRC) or with a Lynch syndrome - associated cancer: cancer of the endometrium, small bowel, ureter or renal pelvis.
• **one relative should be a first - degree relative of the other two**
• **at least two successive generations should be affected**
• **at least one tumour should be diagnosed before the age of 50 years**
• **FAP should be excluded in the CRC case if any**
• **tumours should be verified by histopathological examination**

In 1997, the Bethesda guidelines (table 4) were developed to identify individuals with CRC who should be tested for microsatellite instability.[30] These guidelines were revised in 2004. The sensitivity and specificity of any one of the revised Bethesda criteria for a diagnosis of Lynch syndrome are 82 and 77 %, respectively.[29] The revised Bethesda guidelines are shown to be an appropriate tool to help in selecting patients for genetic and MSI testing.[31]

Several computational clinical prediction models exist, namely MMR predict, MMRpro and PREMM. These appear superior to existing clinical criteria, including the Amsterdam II and revised Bethesda guidelines, when determining an individual's risk for LS. The overall sensitivity and specificity are above 90% for MMR predict and MMRpro.[32]

Table 4: Revised Bethesda guidelines for testing colorectal tumours for microsatellite instability
1. CRC diagnosed in a patient aged <50 years.
2. Presence of synchronous, metachronous colorectal or other Lynch syndrome‐related tumours, regardless of age.
3. CRC with MSI‐H phenotype diagnosed in a patient aged <60 years.
4. Patient with CRC and a first‐degree relative with a Lynch syndrome-associated tumour*, with one of the cancers diagnosed at age <50 years.
5. Patient with CRC with two or more first‐degree or second‐degree relatives with a Lynch syndrome‐associated tumour*, regardless of age.

*LS-associated tumours include tumours of the colorectum, endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain, small bowel, sebaceous glands, and kerotoacanthomas.

1.5.2 Clinical features

Most patients with Lynch syndrome remain asymptomatic until they present with symptoms of colorectal cancer. Abdominal pain, gastrointestinal bleeding, a change in bowel habits, or loss of weight are often the presenting symptoms. Café au lait spots, cutaneous sebaceous gland tumours and keratoacanthomas are rarely found on physical examination. The colorectal cancers in Lynch syndrome differ from typical sporadic colorectal cancers in location, histology, and natural history.

Individuals with Lynch syndrome tend to present at an earlier age and are at increased risk of synchronous and metachronous colorectal cancer. Metachronous colorectal cancers are new primary cancers diagnosed more than 12 months after the first diagnosis of primary colorectal cancer. In a cohort analysis of 332 subjects with LS who had segmental resections, 74 (22%) were diagnosed with metachronous CRC (incidence rate 23.6; 95%CI 18.8–29.7 per 1000 person-years). Cumulative risk of metachronous CRC was 16% at 10 years, 41% at 20 years and 62% at 30 years after segmental colectomy.[32] Synchronous CRCs are more frequent in LS than in sporadic CRC. Approximately 7% of individuals with Lynch syndrome have more than one cancer by the time of diagnosis compared to 2.4% of the general population.[33,34]

Adenomas in Lynch syndrome tend to be flatter, are more often more proximal than sporadic adenomas. The development of cancer in LS is predominantly right sided (60-80%) when compared to 30% in sporadic MSI CRCs.[35,36]

1.5.3 Pathological features

Lynch-associated CRCs arise from adenomas but the progression of the adenoma-carcinoma sequence in Lynch syndrome is thought to occur more promptly than in the CIS pathway CRCs, 35 months compared with 10-15 years.[18] Adenomas are more likely to have high-grade dysplasia and/or villous histology as compared with sporadic adenomas.

Histologically Lynch CRCs have the following features; poorly differentiated, tumour-infiltrating lymphocytes, Crohn's like inflammatory reaction, mucinous, signet ring cells and medullary growth pattern. Despite these histological features, typically associated with a poorer prognosis, and the rapid progression of the adenoma–carcinoma, Lynch-associated CRCs appear to have a better prognosis than the typical sporadic CRCs.

Tumour genetics in Lynch-associated CRCs also differ fundamentally from CIN CRCs. Deficient mismatch repair is manifest as multiple changes of length mutations in nucleotide repeat sequences of tumour DNA when compared to normal mucosa of the same patient, termed high frequency microsatellite instability (MSI-H). MSI testing is performed using polymerase chain reaction (PCR) to amplify a standard panel of DNA sequences containing nucleotide repeats. MSI-H is found in over 90–95% of colorectal cancers occurring as a consequence of Lynch syndrome.[32,37] The sensitivity of MSI testing as a screening tool for LS is about 89% for mutations in MLH1 and MSH2. Mutations in MSH6 and PMS2A have a lower sensitivity, about 77%. Specificity of MSI testing is approximately 90%. [38]

Immunohistochemical analysis of colorectal tumours is widely used for screening for LS. An initial 2-antibody panel has evolved into a 4-antibody panel (MLH1, MSH2, MSH6 and PMS2) detecting mutant MMR polypeptides. The use of immunohistochemistry (IHC) for analysis of tumours for MMR gene proteins has been shown to be a useful alternative to genetic analysis for the identification of MSI in

CRCs.[10] In families with a high probability of having a mutation based on Amsterdam II or revised Bethesda criteria, IHC is the best first step because it may direct genetic mutation analysis.[32] The sensitivity of IHC analysis is about 83% (regardless of the underlying MMR gene mutation), slightly lower than that of MSI analysis.[38]

The high costs of testing all CRCs for MSI or loss of MMR protein (IHC) limits the use of pathological tumour testing as a screening method for LS.[31]

1.6 Genetic testing for Lynch syndrome

1.6.1 Tumour testing

Tumour testing of CRCs by IHC and or testing for MSI can identify patients likely to have LS. The Evaluation of Genomic Application in Practice and Prevention (EGAPP) group from the United States Center for Disease Control and Prevention recommends testing all patients with CRC for LS by IHC or MSI testing. The Multi-Society Task Force endorses the testing of tumours in all patients with CRC 70 years of age or younger. In CRC patients older than 70 years thorough family history is essential for those in whom tumour testing is not done.[31]

1.6.2 Germline testing

In order to establish the diagnosis of Lynch syndrome germline testing for a deleterious mutation in the MMR gene is required. Comprehensive germline testing involves gene sequencing and deletion/duplication DNA analyses so as to detect mutations in mismatch repair genes (MLH1, MSH2, MSH6, PMS2). Genetic identification of a pathogenic mutation in a LS pedigree assists in determining the status of at-risk family members.

There are varied opinions with regards to germline genetic testing for MMR gene mutation. Traditional indications for LS genetic testing have been developed through authority consensus by several national organisations and associations

In newly diagnosed CRCs, genetic testing for LS is indicated for affected individuals in families meeting Amsterdam I or II criteria or revised Bethesda guidelines, those with microsatellite unstable tumours by MSI/IHC testing, or individuals with >5%

chance of gene mutation by computer modelling.

In known mutation positive families, identification of individuals with or without the mutation is possible by DNA testing. Any first-degree relative of individuals with a known MMR/EPCAM gene mutation should undergo site-specific genetic testing for the mutation known to the pedigree.[31]

1.7 Colorectal cancer screening and surveillance in Lynch syndrome

1.7.1 Screening and surveillance colonoscopy

A screening colonoscopy is an examination performed on an asymptomatic person for the purpose of testing for the presence of colorectal cancer or colorectal polyps. Screening is based on risk of CRC determined by family history or genetic testing. Patients with a history of colonic polyps undergo surveillance colonoscopy at varying ages and intervals based on the patient's personal history of polyps, colorectal cancer, and/or gastrointestinal disease. Due to the high incidence of right-sided colonic polyps and cancers in LS adequate bowel preparation is essential in detecting these lesions.

1.7.2 Guidelines for screening and surveillance

The characteristic clinical and pathological features of these malignancies guide the prevention of CRC in LS families. A younger age of presentation, the predominance of right-sided colon cancers, and the rapid polyp growth with shorter time to malignant conversion indicate a need for further investigation. Studies have shown that the adenoma miss rate in LS carriers with conventional colonoscopy is more than 50%, and that many of these missed lesions are small, flat adenomas.[40] Improved detection of small lesions by adequate bowel preparation is particularly important anticipating the accelerated carcinogenesis in LS. The use of intensive inspection (lasting >20 min), narrow band imaging and autofluorescence endoscopy has been suggested to be more effective than standard colonoscopy in preventing CRC in LS.[41]

Colorectal surveillance is the only surveillance protocol in Lynch syndrome proven to reduce CRC incidence, tumour stage and CRC-specific and overall mortality. There is however scant data offering guidelines for colonoscopic screening and surveillance in

patients with a known mutation. Current guidelines are largely based on expert opinion and limited observational data. Multiple studies have evidenced the efficiency of colorectal screening in decreasing CRC mortality (table 5).[41–47]

Initial studies by Finnish group Järvinen *et al* showed a 62% reduction in CRC after 10 years of surveillance when compared to the group that declined colonoscopy surveillance.[42] In their 15-year follow-up, colonoscopic screening at 3-year intervals showed a reduced overall mortality by about 65% in mutation-positive families.[48] Although a 3-year interval between colonoscopies has been proved to be effective[42] more recent studies have noted a significant number of interval CRC developing within 1-2 years of a normal colonoscopy.[41,46,47] Mecklin *et al* showed a 13.5% rate of interval CRC with screening colonoscopy every 2-3 years.[45] Of the 21 CRCs detected by Stuckless *et al,* 8 were within 2 years of a normal colonoscopy.[41] Further studies showed similar results, 13 of 34 and 16 of 33 interval CRCs were diagnosed within 2 years of a previously normal screening colonoscopy.[47,49] Engel's prospective cohort study that included 1126 individuals from families with Lynch syndrome found the median time between the CRCs detected through follow-up colonoscopy and the preceding colonoscopy was less than 1 year (11.3 months).[46] The proportion of interval cancers with a local tumour (Dukes A or B) varied from 78% to 95%. In all studies most interval cancers were diagnosed in individuals older than 40 years. Mecklin *et al,* however, showed that 20–30% of interval CRCs were diagnosed between the age of 30 and 40 years.[45]

In 2014 the US Multi-Society Task Force on Colorectal Cancer published consensus guidelines for screening of high-risk individuals, these were in line with international consensus groups.[31,39,50] Suggested screening for individuals with Lynch syndrome (known MMR/EPCAM mutation carriers) comprises colonoscopy every one to two years beginning at age 20 to 25 years, or two to five years prior to the earliest age of CRC diagnosis in the family (whichever is earlier). Families with MSH6 and PMS2 mutations have been shown to have a lower-risk phenotype with a lesser risk of colorectal cancer and a later age at CRC diagnosis,[21] thus colonoscopic screening is recommended to begin at age 25 to 30 or two to five years prior to the earliest CRC. The identification of cancers before age 30 in these mutation carriers has recently prompted the NCCN to retract its recommendation to start screening patients with

MSH6 and PMS2 mutations at a later age.[51] Screening recommendations, starting at age 25 – 30, remain the same regardless of the causative gene.

Table 5: Intervals and outcomes of colorectal cancer surveillance in Lynch syndrome

	No of participants	Screening interval (yrs)	CRC mortality	Early Stage (Dukes A,B) %
Järvinen *et al* 1995[42]	133	3	0 deaths	100
De Vos tot Nederveen Cappel *et al* 2002[43]	857	<2	Not reported	93
Dove-Edwin *et al* 2005[44]	554	3-5	72% reduced mortality	Not reported
Mecklin *et al* 2007[45]	420	2-3	5 deaths*	80
Engel *et al* 2010[46]	1126	1	Not reported	95
Vasen *et al* 2010[47]	745	1-2	0 deaths	90
Stuckless *et al* 2012[41]	152	1-2	11 deaths*	77

*deaths associated with patient delayed diagnosis, due to poor compliance

1.7.3 Adherence to surveillance colonoscopy

Compliance with the recommended surveillance interval in a number of studies in

developed countries has been shown to be poor. In Europe and the United States compliance with surveillance varies between 58 and 93% in HNPCC family members.[41,52–54] Solitary small studies have proposed that numerous individuals at risk for CRC do not have endoscopic surveillance as frequently as guidelines specify. Vasen *et al* and Stuckless *et al* showed noncompliance rates of 20% and 42% respectively.[41,47] This is worrisome considering lack of participation in a colonic surveillance programme has shown to be associated with increased mortality due to CRC.[42,45–47]

Attendance rates for endoscopic surveillance, used to define compliance, have varied from study to study thus making assessment of compliance complex. Research groups determining compliance rates have determined compliance based on participant attendance at one surveillance endoscopy only, presence within the last 2 years or have categorised compliance based on general surveillance intervals.[47,53–55]

CRC screening studies in U.S. populations have recognised numerous factors related to improved screening commitment. Level of education, income, having health insurance, participating in other cancer screening tests, and receiving a recommendation from their physician for CRC screening improves uptake.[56] A strong association has been observed between CRC screening uptake and the number of times a patient has seen a physician or been in contact with the health system.[56] Compliance with appropriate surveillance for CRC in Lynch syndrome is shown to be higher among individuals with a personal history of CRC and those with a first degree relative with CRC at age <50.[53] Genetic counselling and testing of patients prior to diagnosing LS has shown to significantly influence adherence to recommendations for colon cancer surveillance.[53,57,58]

Multiple justifications have been realised to account for noncompliance to CRC screening. It is unclear whether unsatisfactory CRC surveillance is the result of patient non-compliance or improper physician recommendation for surveillance intervals. Stoffel *et al* noted that physician recommendations for less frequent colonoscopies appeared to be an important reason why subjects had colonoscopies less frequently than every 1–2 years and recommended physician communication as an important target for intervention.[53] Delays due to incorrect interval planning and incorrectly discharging patients from surveillance have also impacted regular attendance of LS

patients.[53] Hospital system errors have included delays in booking by endoscopy departments and the automatic discharge of patients if they failed to respond or attend.[54]

Patient related non-attendance reasons have regularly included fear of discomfort or pain. A large Finnish study of 415 high risk patients undergoing surveillance found that painful experience of colonoscopy, especially in females, was seen as the primary risk for poor compliance.[53,54,59] The financial liability of regular surveillance, nonresponse to contact from endoscopy departments, change of address without informing the hospital, and being pregnant or breastfeeding at the time of scheduled surveillance are also noted as grounds for poor attendance.[53,54] Repeated delays in endoscopic surveillance seem to be related to particular patients who are noncompliant.

1.7.4 Influence of communication on adherence to surveillance

Effective communication occurs when a desired effect is the result of information sharing. It has been shown that effective clinician-patient communication is directly linked to improved patient satisfaction, adherence, and subsequently, health outcomes.[60]

There are no studies reviewing the effects of direct communication on endoscopic surveillance in patients with Lynch syndrome. Data gathered relates to screening and surveillance of colorectal cancer in population-risk individuals. Patient contact methods have varied among research groups, with primary outcome measures predominantly being attendance or uptake of the indicated screening modality. Similarly, screening modalities also varied amongst research groups. Colonoscopy, flexible sigmoidoscopy and faecal occult blood tests (FOBT) are all noted as appropriate screening methods for CRC.

A systematic review by Brouwers *et al* found that client reminders, small media (educational pamphlets, videos or websites), and provider audit and feedback appear to be reasonable strategies to increase the uptake of screening. Group and one-on-one educational intervention showed potential in increasing the uptake of CRC screening.[61] A recent review from the Community Preventive Services Task Force

found robust evidence to support multicomponent interventions to improve CRC screening. Multi-component interventions include a combination of at least two interventions, to increase community demand, increase community access or to increase provider delivery of screening services.[62] A large US randomised controlled trial of 21,860 patients demonstrated that personalised mailings to individual patients produced a modest increase in colorectal cancer screening. Once appropriately informed, most patients opt to be screened for colorectal cancer.[63]

Colonoscopy adherence is often noted to be negatively affected by the painful experience of the investigation.[53,54,59] Voiosu *et al* found that better interaction with patients prior to colonoscopy reduced the patient perceived burden of the investigation. Comfort during colonoscopy and the probability of better attendance is dependent on satisfaction with the information provided before the procedure.[64] Turner *et al* compared telephonic peer coach support with mailed professional brochures to promote attendance to colonoscopy screening. They found that for patients who often fail to keep appointments, peer coach support appears to benefit colonoscopy attendance more than an educational brochure.[65]

The field of cross-cultural care focuses on the ability to communicate effectively and provide quality health care to patients from diverse sociocultural backgrounds. There is no empirical literature comparing the effectiveness of different models of cross-cultural care and communication.[66] In low-income minorities compliance with screening colonoscopy was improved by patient navigators to personally assist with overcoming organisational barriers.[67]

Available data underscores the fact that informed patients can play an active role in achieving effective adherence to preventive services.

1.8 Lynch syndrome in South Africa

The first clinical description of LS in South Africa was in 1985. The diagnosis was based on an affected 30-year-old man who had developed colorectal cancer at the age of 19, and a detailed family pedigree showing autosomal dominant inheritance over three generations.[68]

Data pertaining to Lynch syndrome within South Africa is sparse. The majority of this

data is related to a cohort of over 100 individuals with Lynch syndrome that have been identified by genetic testing of at-risk family members in the Northern Cape.

1.8.1 Colorectal cancer screening and surveillance

The Annual Northern Cape Colonoscopy Outreach program undertakes this platform intending to provide an annual mobile genetic testing and surveillance service in small district hospitals and clinics along the western coast of SA. At the age of 18 relatives of known LS individuals undergo genetic counselling and site-specific testing to ascertain a possible causative mutation. Patients identified as having an MMR gene mutation undergo yearly surveillance colonoscopy every 2 years starting at age 18, then annually from 30 years old. The mobile colonoscopy unit has shown to provide quality care for LS families in remote areas of South Africa.[69]

In a study done by the University of Cape Town on previously identified families living in the Northern Cape Province, surveillance colonoscopy was coupled to improved overall, and CRC-related survival, in subjects carrying a single MMR gene mutation.[55] In line with international findings, polyp pick-up is most predominant in the right-sided colon thus highlighting the significance of appropriate and comprehensive colon preparation prior to endoscopy.[69]

1.8.2 Adherence to surveillance colonoscopy

With each year of colonoscopy surveillance in the Northern Cape Province documentation of attendance is noted. Over the past years attendance at this outreach clinic has been less than desired. In 2007 Bruwer *et al* documented poor uptake to colonoscopy surveillance. It was noted that fewer than a quarter of participants, attending for surveillance, had been adherent with all their recommended screening appointments.[1] Major factors identified for noncompliance were financial constraints (18%) and transport related difficulties (16.4%). Unlike findings in international literature, the unpleasant experience of bowel preparation was found to have a significant negative impact adherence to surveillance (16.4%). In line with international findings, 16.8% of patients reported colonoscopy as uncomfortable and 28.8% reported the investigation to be a painful experience. This however did not

translate to a cause for poor adherence, only 4.9% of patients reported pain as a reason for nonattendance.

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Chapter 2 – Publication-ready manuscript

Introduction

Hereditary non-polyposis colorectal cancer (HNPCC), now known as Lynch syndrome when there is a known causative mutation, is the most prevalent of the inherited colon cancer susceptibility syndromes. Lynch syndrome is an autosomal dominant condition caused by a germline mutation in one of several DNA mismatch repair (MMR) genes. It is characterised by the development of colorectal, endometrial and various other cancers at a young age, with individuals at risk for synchronous and metachronous colorectal cancer (CRC) [2]. The lifetime risk of developing CRC is significantly higher in Lynch syndrome, and varied risk is seen with each genotype mutation. Lynch syndrome is shown to account for 2 to 3 per cent of all colon cancer cases in high incidence areas [3]. The adenoma-carcinoma sequence is thought to progress more precipitously in Lynch syndrome and new cancers have occurred within one to two years after what appeared to be a normal colonoscopy [4]. In Lynch syndrome, adenomas tend to be flatter, are more often proximal, and more commonly have high-grade dysplasia and/or villous histology than sporadic adenomas. Like the adenomas, CRCs in Lynch syndrome are also more commonly proximal, thus highlighting the need for complete bowel preparation [5].

In the Northern Cape Province, the annual incidence of colorectal cancer is 3.7/100 000 population [6]. There is evidence that inherited colorectal cancer may account for a greater proportion of the disease burden in this population than would be expected [7].

Endoscopic surveillance is the only surveillance protocol in Lynch syndrome proven to reduce CRC incidence, tumour stage and CRC-specific and overall mortality [5,8-10]. Limited data is available offering guidelines for colonoscopic screening and surveillance in patients with a known Lynch mutation. Current guidelines are largely based on expert opinion and limited observational data. In 2014 the US Multi-Society Task Force on Colorectal Cancer published consensus guidelines for screening of high-risk individuals. These guidelines are in line with international consensus groups

[2,11,12]. Suggested screening for individuals with Lynch syndrome comprises colonoscopy every one to two years beginning at age 20 to 25 years, or two to five years prior to the earliest age of CRC diagnosis in the family (whichever is earlier) [2].

There are no studies reviewing the effects of direct communication on endoscopic surveillance in patients with Lynch syndrome. Data gathered relates to screening and surveillance of CRC in population-risk individuals. Patient contact methods have varied among research groups, with primary outcome measures predominantly being attendance or uptake of the indicated screening modality [13,14]. Available data underscores the fact that informed patients can play an active role in achieving effective adherence to preventive services [15-17].

Since 1988, the University of Cape Town and Groote Schuur Hospital has offered surveillance colonoscopy to high–risk individuals along the west coast and in the Northern Cape Province of South Africa. Initially surveillance was provided for suspected high–risk families based on family history. Mutational analysis was introduced in 1997 and this has led to the detection of 17 mutations in the MLH1 and MSH2 genes in 56 families [6,18]. One MLH1 mutation is common to 32 families and accounts for over 100 individuals identified with Lynch syndrome who require annual colonoscopic surveillance in the Northern Cape Province [18]. Annual colonoscopy in these subjects, carrying a single MMR gene mutation, has shown to be associated with improved overall and CRC-related survival [19]. The mobile service has shown to provide access to colonoscopy in remote areas without compromising the quality of service [20].

Until now, biannual visits to the Northern Cape Province have been undertaken. Surveillance colonoscopy is done in August/September of every year and is preceded a by a preparation visit approximately 6-8 weeks prior to surveillance. The Annual Northern Cape Colonoscopy Outreach takes place over one week in four pre-determined towns along the western coast of South Africa. The outreach colonoscopy service requires that all equipment and trained staff be provided as a mobile service. In order to aid attendance, prearranged transport has regularly been available to those individuals who do not have their own. Over the past few years it has been noted that fewer than 25 % of the total participants obtained 100 % adherence to colonoscopy screening. A significant number of individuals (16.4%) reported poor adherence to

bowel preparation as a reason for noncompliance with surveillance [1]. The preceding preparation visit was designed to directly impart information to participants undergoing regular surveillance as well as to deliver bowel preparation to rural areas (Fig. 3). In addition, new family members are identified for genetic counselling and testing of founder mutations. Effective clinician-patient communication is shown to be directly linked to improved patient satisfaction, adherence, and subsequently, health outcomes [20]. Each year an attempt is made to personally interact with and supply every at-risk individual with information pamphlets, in their preferred language, pertaining to colonoscopy preparation and the importance of adherence.

The Northern Cape Province is the largest and most sparsely populated province of South Africa. Afrikaans first-language speakers predominate, about 68% of the population, with other primary languages being English, Setswana and Xhosa. During the preparation trip the team covers approximately two thousand kilometres in an attempt to reach all individuals scheduled for surveillance. It has been logistically impossible to cover the entire area in one week and inevitably every year some areas are not visited. This results in some patients receiving information with direct interaction from the team where as others receive the same information, as pamphlets alone, from medical staffs at local clinics. The current standard of care involves visiting as many towns as practical. It is chance, finance and logistic difficulties that dictate whether subjects are visited during the preparation trip or not.

The primary objective of this study was to determine whether there is a need for a yearly colonoscopy preparation visit to high–risk individuals in the Northern Cape Province. This study determines whether direct interaction with patients prior to surveillance colonoscopy will significantly impact attendance. The primary end point is measured by attendance at surveillance colonoscopy in September of the same year. Secondarily the adequacy of colonic preparation was evaluated.

Methods

Study design

A randomised controlled crossover trial was developed to take place over two years of

endoscopic surveillance by the Annual Northern Cape Colonoscopy Outreach Program. The trial period extended from July 2014 to September 2015, and involved four trips to the Northern Cape Province (2 preparation and 2 surveillance colonoscopy trips).

Participants were selected from a cohort of 102 patients known and managed through the Colorectal Surgery Unit at Groote Schuur Hospital and the Division of Human Genetics at the University of Cape Town. Included participants were randomised to a control group that was not seen prior to colonoscopy, and a test group that was visited by a team from Cape Town in July of each study year. Randomising individuals was impractical as many were family members residing together. Randomisation was therefore achieved by dividing individuals into small groups of 5-10 based on area of residence (table 6).

These smaller 'town groups' were then randomised to control and intervention groups. Randomisation was done by blindly withdrawing numbered town groups from a sealed container. Town groups 1, 2, 4, 5, 6 and 9 formed the control group (Group A) in 2014. In the first year of study the control group of individuals had bowel preparation and instructions forwarded to local clinics. The clinics were asked to contact the participants and provide them with the required written information prior to their surveillance appointment. In July 2014, the intervention group (Group B) of individuals (town groups 3, 7, 8, 10, 11 and 12) were visited at their hometowns and personally provided with instructions and bowel preparation by the research team. In the second year of study the intervention on these groups was reversed.

The majority of participants speak Afrikaans as a home language, thus all verbal and written communication was accomplished in each individuals preferred language. Consent was obtained from all individuals participating in this trial. This study adheres to the 2013 Helsinki Declaration and was approved by the University of Cape Town Human Research Ethics Committee (HREC REF: 352/2014).

Inclusion and exclusion criteria

All subjects undergoing surveillance colonoscopy, known to have a genetic mutation predisposing them to colon cancer, and had an intact colon, were included in this trial.

Individuals undergoing surveillance biannually were excluded. Participants undergoing colonic surgery within the study period were included in the primary outcome measure and excluded from secondary outcomes.

Outcome measures

Compliance and understanding of information given was measured in terms of attendance at the Annual Northern Cape Colonoscopy Outreach visit in September of each year of study. Adequacy of bowel preparation was assessed during colonoscopy by means of the Harefield Cleansing Scale [22]. (Fig. 4)

Demographic, socio-economic, and clinical data were extracted from patient folders and recorded on an Excel data-capturing sheet. This included all patients who attended, as well as those who were expected to attend surveillance in each year of study.

The personal experience of patients was reviewed by the completion of evaluation forms by those who attended colonoscopy screening in September 2014 and 2015.

Statistical considerations

A power study was done to determine sample size required for a study power of 90% (Fig. 5). This was based on the research team proposal that 70% of subjects would attend if personally visited during the preparation trip and 50% if they were not visited. With the consideration that this is a superiority trial, it was calculated that a total of 66 individuals (33 in each arm) were required to have a 90% chance of detecting, as significant at the 5% level, an increase in the primary outcome measure from 50% in the control group to 70% in the experimental group. A correlation assumption, using McNemar's test, of 0.5 based on the proposal of attendance also correlates to a total of 66 patients required to detect significance.

Statistical analysis was performed using Stata. Categorical variables of both arms are compared using correlates to a total of 66 patients required to detect. McNemar's, Mainland-Gart and Prescott's tests assess the treatment and period effects of crossover.

Results

We identified 56 families with a MMR germline mutation encompassing 102 individual mutation carriers living in the Northern Cape Province and requiring annual surveillance. Twenty-three patients were excluded from the study as they had previously undergone colonic surgery, only requiring surveillance by flexible sigmoidoscopy. One patient died prior to the start date of the trial. Of the initial 102 individuals identified to take part, seventy-eight (76.4%) were eligible for the trial. All participants contacted by the study coordinator, and subsequently by the researcher, agreed to participate. Figure 6 shows the patient flow through the clinical protocol. Two patients who presented for surveillance colonoscopy in 2015 did not undergo colonoscopy due to poor health. Three patients underwent colonic surgery within the two years of study. All three of these participants presented for surveillance in 2015 and underwent flexible sigmoidoscopy. The study cohort consisted of 28 (36%) male and 50 (64%) female participants aged between 25 and 78 years (median 39.5 years). Groups A and B consisted of 38 and 40 participants respectively.

The baseline demographic characteristics of the randomised patients are shown in table 7. There were no significant participant baseline differences between the two groups. Several participants living in rural Northern Cape towns were required to travel long distances to attend surveillance. The majority of participants (83.33%) necessitated a commute of up to 200 kilometres in order to attend annual surveillance. Forty-nine (62.82%) participants required arranged transport to travel from their hometown to the pre-determined location of outreach surveillance colonoscopy.

On analysis of medical records, 85% of participants had attended at least one of their previously scheduled colonoscopy appointments. Of the 78 participants, only 51% attended surveillance colonoscopy in 2013, the year preceding this study.

Primary outcome analysis

In September 2014 36 (46.2%) participants presented for annual surveillance colonoscopy. Of the thirty-six individuals presenting 19 were from the control group (Group A) and 17 from the intervention group (Group B). Hence, 50% of individuals

receiving indirect contact, and 42.5% of individuals directly contacted prior to surveillance attended. In 2015, there were 41 (53%) compliant individuals; this included 21 (55%) individuals receiving a preparatory direct contact visit (Group A), and 20 (50%) individuals from the 2015 control group B.

Twenty-seven (34.6%) of the 78 individuals presented for surveillance in both years of study, 14 from Group A and 13 from Group B. Twenty-eight (35.9%) participants did not attend both appointments. Group A, initially the control group, showed an increase in attendance to surveillance from 50% in 2014 up to 55% with intervention in 2015. Group B also showed an improved compliance in 2015, 42.5% to 50%, despite receiving intervention by direct contact in 2014 (Fig. 7).

The period by treatment interaction was measured to exclude carry-over effect. Pearson's chi square (one degree of freedom) and Fisher's exact test of association revealed p-values of 0.504 and 0.593 respectively (odds ratio (OR) 1.131). This result suggests no interaction. Calculation of the period effect of crossover suggests no period effect significance (P = 0.297).

Assuming the absence of a carry-over effect and a period effect, the treatment effect was assessed by means of McNemar's test. A p-value of 0.835 suggests there was no effect after intervention by the research team. This was confirmed by the Mainland-Gart (P = 0.795) and Prescott tests of association (P = 0.855).

Factors influencing primary outcomes

Table 8 shows the effects of variables on the primary outcome. Age and gender showed no statistically significant impact on attendance to endoscopic surveillance. Although not statistically significant (P = 0.095), patients travelling shorter distances showed an inclination towards reduced attendance. Individuals having attended previously scheduled appointments were more likely to be compliant during the study period (P = 0.001; 95% confidence interval (CI)).

Participants having attended more than 5 previous colonoscopies showed 54.2% attendance over two years. Those having undergone more than 10 prior surveillance scopes achieved 87.5% attendance (Fig. 8).

Secondary outcome analysis

Seventy-seven participants were analysed for secondary outcomes, 36 in 2014 and 41 in 2015. A total of 72 colonoscopies were done throughout the study period (Fig. 9). All of the 36 individuals attending surveillance in 2014 underwent colonoscopy. In 2015, 36 of the 41 individuals attending underwent colonoscopy. As mentioned, five individuals were excluded from colonoscopy in 2015 despite having attended their appointment (2 from Group A, 3 from Group B).

In 2014 and 2015 respectively, 34 of 36 (94.44%) and 35 of 36 (97.22%) individuals undergoing colonoscopy had been adequately prepared (Harefield A or B). In 2014 100% of individuals in the control group, not receiving direct contact, achieved adequate colonic preparation. There were only 3 failed colonoscopies due to poor preparation (Harefield C or D). Two of the failed colonoscopies belonged to the intervention group receiving direct contact prior to surveillance in 2014.

Patient comment

Fifty individuals supplied questionnaires for assessment. The majority of participants (96%) were satisfied with the information provided by brochures, regarding the communication adequate. Only 2 patients reported poor understanding of the provided written material. Despite considering the small media adequate, 22 individuals (44%) requested to be directly contacted by a doctor or nurse prior to surveillance colonoscopy.

Upon assessment of self-reported motives for prior non-attendance the research group found that, of the 50 individuals, only 26 (52%) supplied reasons for not attending previously scheduled colonoscopy appointments. Ten individuals reported an unwillingness to undergo annual surveillance, presenting for appointments only when convenient. Five participants defaulted due to work commitments and 4 reported being ill on the date of scheduled surveillance. Two individuals were pregnant at the time of surveillance and one was incarcerated. Only three individuals reported an unpleasant prior experience as motive for non-compliance. Of these three, 2 reported bowel preparation to be intolerable. One patient did not attend because she was scared.

Discussion

The results of this study demonstrate that 34.6% of the study population are compliant with the screening intervals suggested by consensus groups [2,11,12]. This is lower than European and United States compliance rates with surveillance varying between 58% and 93% in Lynch syndrome family members [23-26]. Vasen et al and Stuckless et al reported noncompliance rates of 20% and 42% respectively [10,24].

Direct contact with known Lynch syndrome individuals did not significantly improve adherence to surveillance (P = 0.835). Counselling and the provision of pertinent information by the research group 6 weeks prior to surveillance was not shown to improve attendance. In a systematic review by Brouwers *et al* client reminders and small media (educational pamphlets, videos or websites) appeared to be reasonable strategies to increase the uptake of screening. Group and one-on-one educational intervention showed potential in increasing the uptake of CRC screening [13]. In addition to annual counselling prior to surveillance all participating individuals have previously undergone genetic counselling and testing, thus were expected to have improved adherence to recommendations for CRC surveillance. Genetic testing in Lynch syndrome has shown to considerably improve compliance with CRC surveillance [25,27,28].

Available data underscores the fact that informed patients can play an active role in achieving effective adherence to preventive services, however the research intervention did not result in improved uptake. The probability of better attendance is likewise shown to be dependent on satisfaction with the information provided before the procedure [29]. The information provided at direct contact has been reviewed by the research team and found to be appropriate and given in each individual's home language. Patient self-reports on the adequacy of information supplied showed that 96% of participants understood the educational pamphlets provided. Despite reportedly understanding the pamphlets, almost half of the participants (44%) found it useful to directly interact with a health care provider prior to surveillance colonoscopy. This may indicate a need for better verbal communication with individuals undergoing CRC surveillance.

With advances in telecommunication infrastructure, particularly cellular messaging systems, in rural areas of South Africa, the research team has noted improved access to indirect communication within the study population. This may explain why intervention by direct contact showed no significant improvement in attendance.

Inconsistent with previously published international literature regarding CRC screening, we have shown that surveillance adherence in known Lynch individuals in South Africa's Northern Cape Province is not influenced by gender or age. Internationally, significantly more female mutation carriers less than 60 years of age have shown to take up and adhere to surveillance [24,30].

Reduced health care coverage in rural areas has shown to adversely influence CRC screening uptake, however unpredictably, individuals travelling shorter distances showed an inclination towards reduced attendance. This may be due to pre-planned transport for individuals travelling from more remote areas. As noted in low-income minorities, compliance with screening colonoscopy was improved by personal assistance with overcoming organisational barriers [17].

In-line with international findings a strong association has been observed between CRC surveillance uptake and the number of times a patient has seen a physician or been in contact with the health system [30]. In our cohort, patients known with prior satisfactory compliance were likely to retain their compliance. Compliance was noted to range from 15.1% in individuals with no or one prior surveillance colonoscopy, to 87.5% in those having attended more than ten previous appointments. Prior compliance was the only variable shown to significantly influence attendance ($P = 0.001$). Repeated delays in endoscopic surveillance seem to be related to particular patients who are non-compliant. This allows for identification and redirection of resources towards individuals requiring additional information and supportive counselling.

Major factors previously identified for non-compliance in this study population were financial constraints (18%) and transport related difficulties (16.4%). In addition, 16.8% of patients reported colonoscopy as uncomfortable and 28.8% reported the investigation to be a painful experience [1]. Patient related non-attendance reasons have regularly included fear of discomfort or pain [25,26,31]. A large Finnish study of 415 high-risk patients undergoing surveillance found that the painful experience of

colonoscopy, especially in females, was seen as the primary risk for poor compliance [31]. Voiosu *et al* found that better interaction with patients prior to colonoscopy reduced the patient perceived burden of the investigation [29]. We gained insufficient self-reported data from participants to accurately assess reasons for non-compliance.

Bruwer *et al* noted the unpleasant experience of bowel preparation to have a significantly negative impact on adherence to surveillance (16.4%) in this population group [1]. Despite this report, we found only 3 of the 72 (4.17%) colonoscopy outcomes failed due to poor colonic preparation. There was a remarkably positive adherence to bowel preparation in those individuals attending surveillance. In this study only two patients reported not attending surveillance due to poor tolerance of bowel preparation.

We acknowledge there are limitations to our study. Despite the research group's methods to limit interaction between family members we cannot confirm nor exclude that there was communication between individuals living in various towns across the Northern Cape Province. Almost one third of the study group, 27 individuals not presenting for surveillance in both study years, did not participate in subjective evaluations of justifications for non-compliance. Thus, the research team cannot accurately comment on the reasons for non-attendance in this study.

Conclusion

Direct interaction with Lynch syndrome individuals prior to annual surveillance colonoscopy has not shown to positively influence attendance. In the setting of limited resources within a large area of distribution, efforts to improve CRC surveillance need to be better focused. Yearly indirect contact with individuals known to be compliant appears to be an adequate method of retaining adherence. The Annual Northern Cape Colonoscopy Outreach program's preparation trip should focus on interaction and counselling directed at individuals identified to be defaulting surveillance.

Tables and figures

Table 6: Participant grouping as per Northern Cape towns

Group number	Town groupings	Number of subjects	Intervention year
1	Upington	7	2015
2	Kakamas	5	2015
3	Buffelsrivier +Aggenys	9	2014
4	Keimoes + Britstown + Brandvlei + Vanrhynsdorp	6	2015
5	Garies + Hondeklip Bay + Lelifontein	8	2015
6	Steinkopf	5	2015
7	Okiep + Eksteenfontein + Springbok	7	2014
8	Kommagas	9	2014
9	Port Nolloth + Nababeep	7	2015
10	Kharkhams + Nourivier	6	2014
11	Clanwilliam + Vredendal	4	2014
12	Lutzville	5	2014

Table 7: Participant demographics by intervention group

	Group A (n=38)	Group B (n=40)	Total (n=78)
Male	34.21%(13)	37.5%(15)	35.9%(28)
Female	65.79%(25)	62.5%(25)	64.1%(50)
Mean age (range)	42.37(25-78)	41.23(25-74)	41.78
Median age (range)	38.5(25-78)	40.5(25-74)	39.5
Travel distance			
Mean (km)	108.34	141,68	125.44
0-50km (n)	26.32%(10)	22.5%(9)	24.36%(19)
50-100km (n)	42.11%(16)	15%(6)	28.2%(22)
100-200km (n)	18.42%(7)	42.5%(17)	30.77%(24)
200-300km (n)	7.89%(3)	12.5%(5)	10.26%(8)
>300km (n)	5.26%(2)	7.5%(3)	6.41%(5)
Transport			
Own (n)	39.47%(15)	35%(14)	37.18%(29)
Prearranged (n)	60.53%(23)	65%(26)	62.82%(49)

Table 8: Effects of variables on primary outcome (95% CI)

	Coefficient	Std. Err.*	p-value
Gender	.058957	.4227125	0.889
Age	.0048007	.0151083	0.751
Previous scopes attended	.1981803	.0586155	0.001
Travel Distance	.0036858	.0022058	0.095

*standard error

Fig. 3: Preparation trip towns in the Northern Cape Province of South Africa

Fig. 4: Schematic of Harefield Cleansing Scale [21]

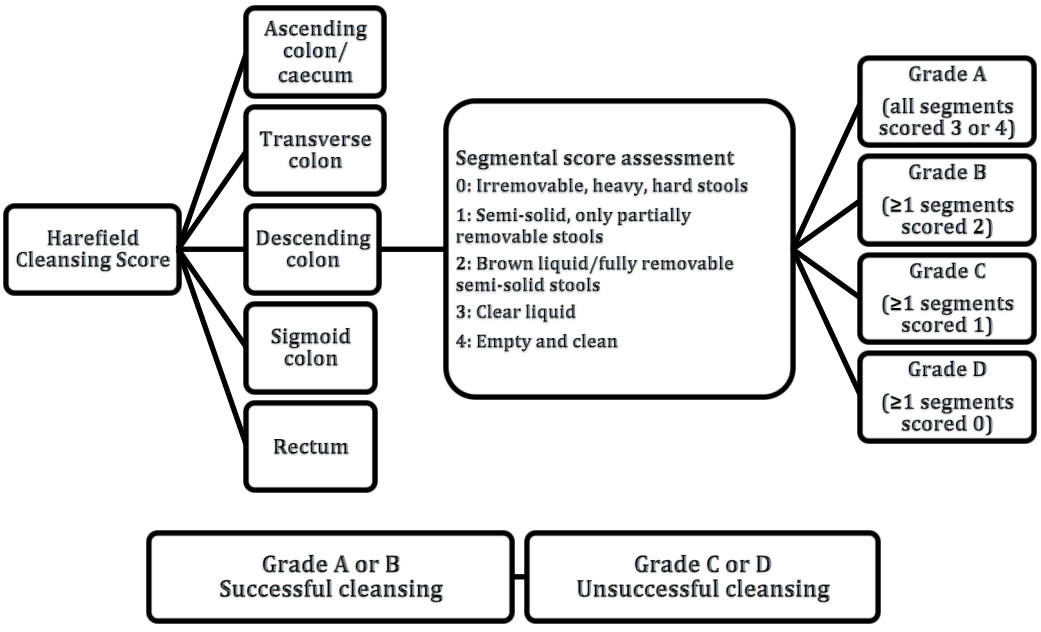


Fig. 5: Sample size required to detect

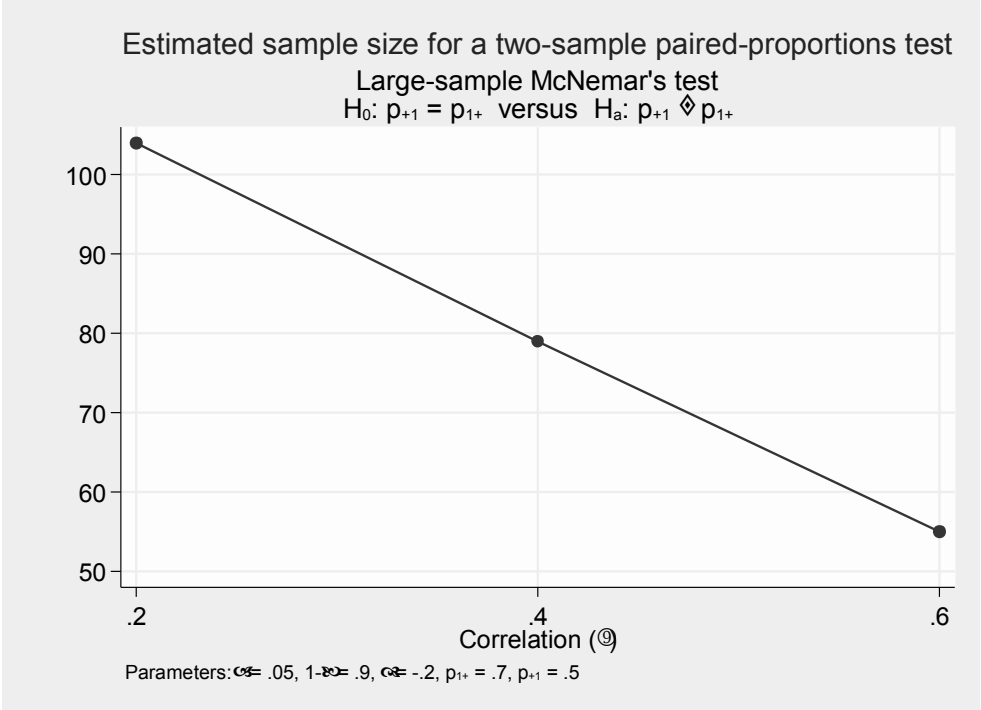


Fig. 6: CONSORT diagram

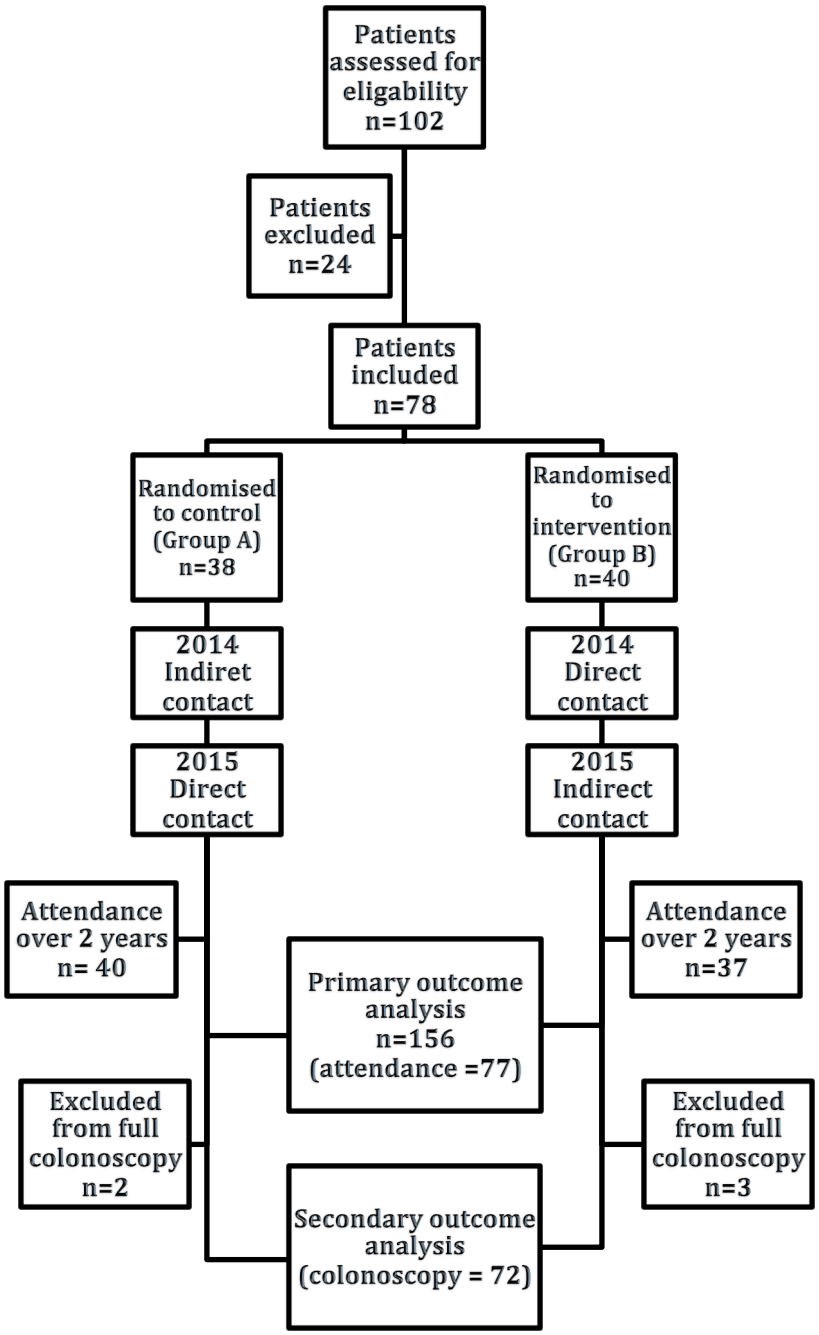


Fig. 7: Primary outcome attendance to surveillance endoscopy

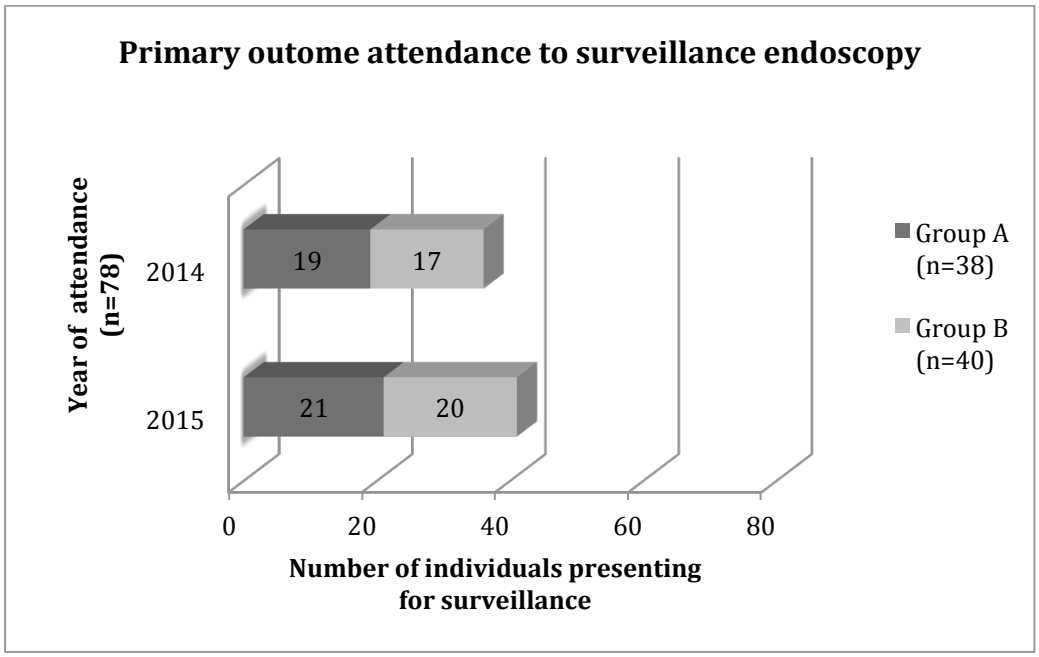


Fig. 8: Individual attendance to surveillance based on prior attendance

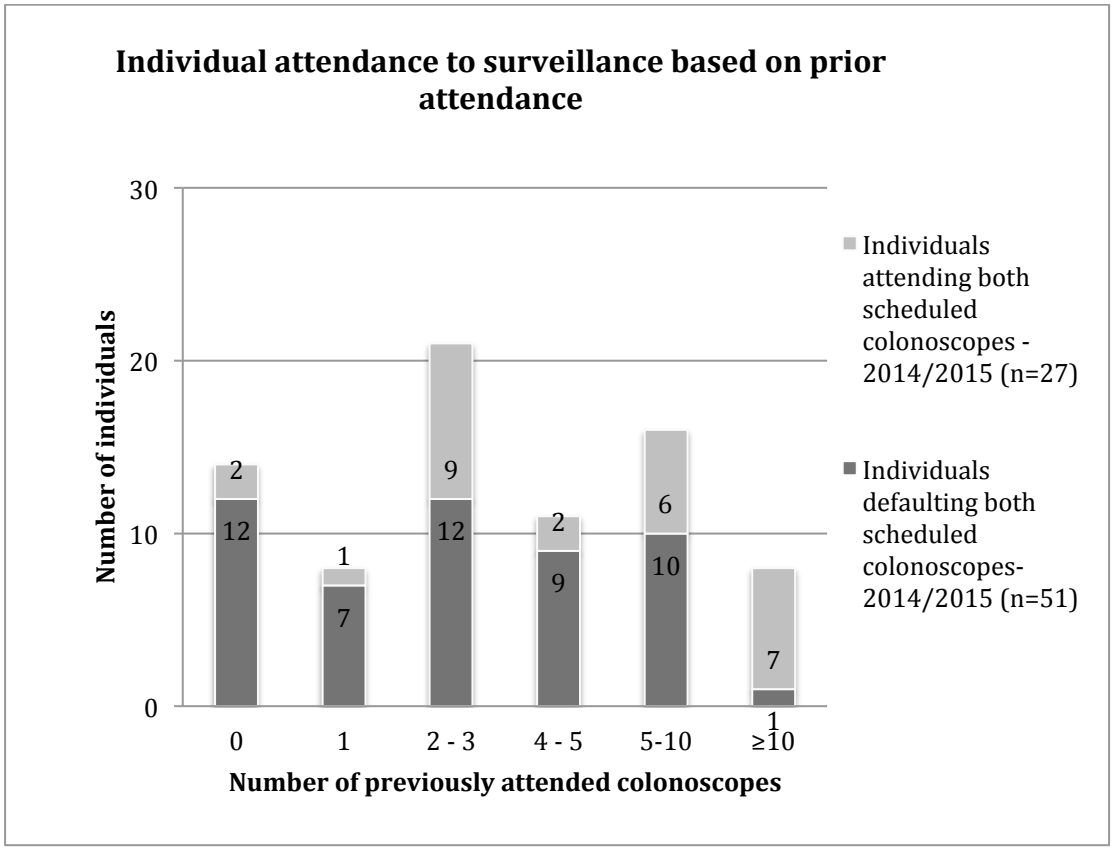
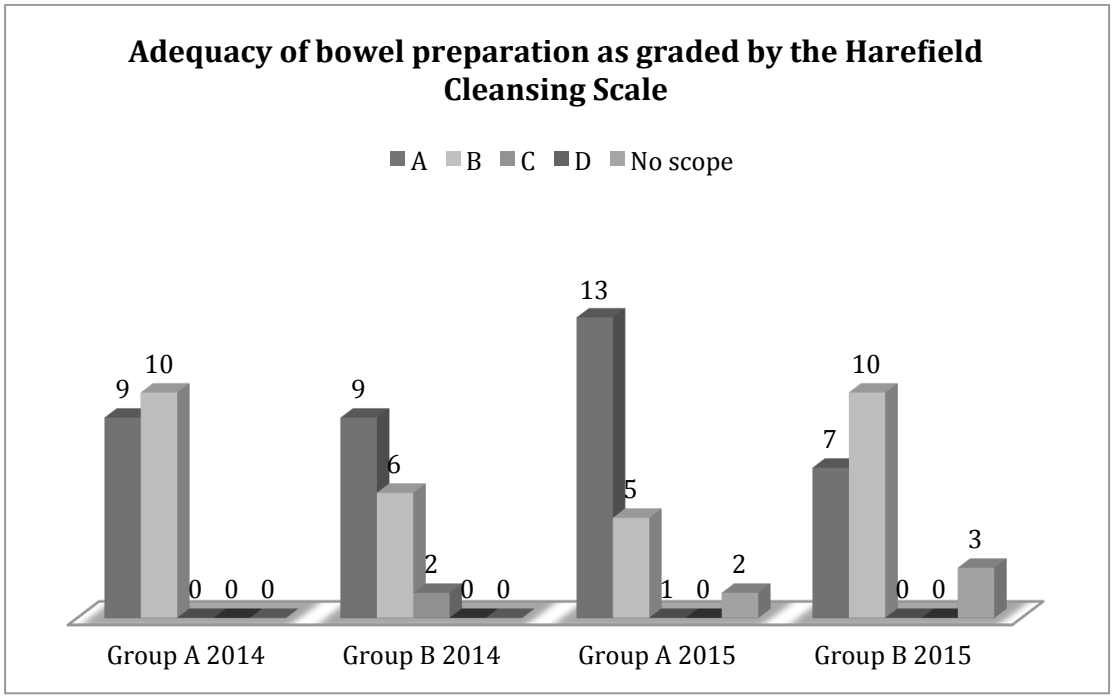


Fig. 9: Adequacy of bowel preparation as graded by the Harefield Cleansing Scale



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Chapter 3 – Appendices

Appendix A - Ethics approval 2015

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

01 June 2015

HREC REF: 352/2014

Prof P Goldberg
Department of Colorectal Surgery
J-45
OMB

Dear Prof Goldberg

PROJECT TITLE: SURVEILLANCE COLONOSCOPY FOR LYNCH SYNDROME IN THE NORTHERN CAPE: DOES DIRECT CONTACT IMPROVE COMPLIANCE? (MMED Candidate - Dr A Coccia)

Thank you for submitting your protocol amendment to the Human Research Ethics Committee (HREC) for review.

Before the amendment can be approved, please address or comment on the following:-

1. The protocol does not include any information that this a now a randomised control cross over study.
2. Please provide the updated informed consent document with this new information.
3. The Helsinki Declaration has been updated to 2013.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Appendix B - Ethics approval 2017 annual update

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE
- 7 FEB 2017
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	28.2.2018
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	pp TBurgess	Date Signed	07/02/2017

Comments to PI from the HREC
Late submission noted TBurgess

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	06/02/2017		
HREC REF Number	352/2014	Current Ethics Approval was granted until	30/6/2018
Protocol title	Surveillance colonoscopy for Lynch Syndrome in the Northern Cape: Does direct contact improve compliance?		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☑ No		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Prof Paul Goldberg		
Department / Office Internal Mail Address	Dept. of Colorectal Surgery paul.goldberg@uct.ac.za		

1.1 Does this protocol receive US Federal funding?	☐ Yes	☑ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☐ No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	☑ No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Appendix C – Consent form

Consent Form to participate in medical research

Surveillance colonoscopy for Lynch Syndrome in the Northern Cape: Does direct contact improve compliance?

Dr. AC Coccia
Supervisor
Prof. PA Goldberg
Department of Colorectal Surgery
Groote Schuur Hospital

Contact for research: Dr. AC Coccia (Tel: 074 124 5542; e-mail: ac_coccia@yahoo.com)

I, _____ hereby agree to participate in the research project evaluating the requirement of a pre-colonoscopy preparation trip. The risks and benefits have been explained to me by Dr. AC Coccia and Sr. Ursula Algar which I understand and have been given the opportunity to ask questions.
I understand that my participation in this study is entirely voluntary.
I understand there will not be any financial compensation involved for participation in this research.
I agree to the use of my medical records which might include a physical examination and personal information. This will remain confidential but may be used for presentations and articles (on an anonymous basis).

_____ _____
Patient Doctor

_____
Witness

_____
Date

Appendix D – Questionnaire

Questionnaire

Patient experience of preparation for colonoscopy

Surveillance colonoscopy for Lynch Syndrome in the Northern Cape: Does direct contact improve compliance?

Dr. AC Coccia

Supervisor
Prof. PA Goldberg
Department of Colorectal Surgery
Groote Schuur Hospital

Please tick the appropriate block

1. Have you ever had a colonoscopy before?

☐Yes ☐No

2. If yes, how many previous screening colonoscopies have you had?

_____

3. Have you attended all your screening colonoscopy appointments?

☐Yes ☐No

4. If not, what was the reason for not attending?

_____.

5. Prior to the colonoscopy, did you receive a pamphlet or booklet explaining what the test involved?

☐Yes ☐No

6. If you did received a pamphlet or booklet:
   a. Did it explain the preparation in a clear manner?

   ☐Yes ☐No

   b. Did it explain the procedure in a clear manner?

   ☐Yes ☐No

7. Did you understand the information given in the pamphlet/booklet?

☐Yes ☐No

8. Prior to the date of your colonoscopy, did you meet with a nurse or doctor from Cape Town?

☐Yes ☐No

9. Did the nurse or doctor discuss with you what the test involved?

☐Yes ☐No

10. If so, was there any additional information given by the nurse or doctor that was not covered in the pamphlet/booklet?

_____

_____

11. Do you feel it would help to have a meeting with a nurse or doctor prior to your colonoscopy?

☐Yes ☐No

12. Would you prefer to have a meeting with a nurse or doctor prior to the date of your colonoscopy?

☐Yes ☐No

Thank you

Appendix E – Instructions to authors

International Journal of Colorectal Disease

Text Formatting

Manuscripts should be submitted in Word.

Use a normal, plain font (e.g., 10-point Times Roman) for text.

Use italics for emphasis.

Use the automatic page numbering function to number the pages.

Do not use field functions.

Use tab stops or other commands for indents, not the space bar.

Use the table function, not spreadsheets, to make tables.

Use the equation editor or MathType for equations.

Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Manuscripts with mathematical content can also be submitted in LaTeX.

LaTeX macro package (zip, 182 kB)

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a

reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols. Always use footnotes instead of endnotes.

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list.

The entries in the list should be numbered consecutively.

Always use the standard abbreviation of a journal's name according to the ISSN List of Title Word Abbreviations.

Tables

All tables are to be numbered using Arabic numerals. Tables should always be cited in text in consecutive numerical order. For each table, please supply a table caption (title)

explaining the components of the table. Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.

Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Figures

To add lettering, it is best to use Helvetica or Arial (sans serif fonts).

Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).

Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.

Avoid effects such as shading, outline letters, etc.

Do not include titles or captions within your illustrations.

All figures are to be numbered using Arabic numerals.

Figures should always be cited in text in consecutive numerical order.

Figure parts should be denoted by lowercase letters (a, b, c, etc.).

If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures, "A1, A2, A3, etc." Figures in online appendices (Electronic Supplementary Material) should, however, be numbered separately.

Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.

Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.

No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.

Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.

Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

Figures should be submitted separately from the text, if possible.

When preparing your figures, size figures to fit in the column width.

Informed consent

The following statement should be included:

Informed consent: “Informed consent was obtained from all individual participants included in the study.”

If identifying information about participants is available in the article, the following statement should be included:

“Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.”