CANCER FREE SURVIVAL IN MUTATION POSITIVE HNPCC INDIVIDUALS WITH COLORECTAL ADENOMATOUS POLYPS IDENTIFIED ON SURVEILLANCE COLONOSCOPY

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DECLARATION

I, ***Oostewalt Swart***, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Glossary of abbreviations

HNPCC – Hereditary nonpolyposis colorectal cancer

CRC – Colorectal cancer

MMR gene – Mismatch repair gene

FAP – Familial Adenomatous Polyposis

IQR – interquartile range

MSH – Mutation S homologue

MLH – Mutation L homologue

MSI – Microsatellite instability

IHC – Immunohistochemistry

5-FU – 5-Fluoro-uracil

GSH – Groote Schuur Hospital

UCT – University of Cape Town

TNM – classification – Tumour, Node, Metastasis-classification

Lynch syndrome family: Causative mutation identified

CHAPTER ONE: Literature Review

1.1 Introduction

The prevalence of colorectal cancer (CRC) places it in the top five cancers worldwide and is the second most common cause of cancer related death. Developed populations have a 5-6% lifetime risk of CRC(1). The South African Cancer Registry (last updated 2004) shows a 1/98 and 1/150 life time risk for developing CRC in males and females respectively (2).

About 20% of all CRC displays some familial tendency, but in less than half of these, there is a proven Mendelian inheritance(1). Hereditary nonpolyposis colorectal cancer (HNPCC) is the most common inherited CRC and accounts for 2-5% of the total CRC burden in the developed world(3)(4)(5).

In 1913 Aldred Warthin documented a family (family G) who appeared to have an inherited pattern to mostly uterine and gastric cancers(6). In 1966 Henry Lynch published his seminal paper about two Midwestern families ("N and M") with a familial grouping of cancers that resembled the syndrome that today carries his name(7).

HNPCC was first identified in South Africa in 1985 by a general practitioner who noted an unusually large number of young patients in family clusters with CRC in the Namaqualand and surrounding areas of the Northern Cape(8). The hereditary risk for CRC in these families was confirmed when the specific genetic mutations responsible were first identified in 1996(9)(10). These families form part of an active genetic screening and colonoscopic surveillance programme led by the Colorectal Surgery Unit and the Department of Human Genetics of the University of Cape Town. Up to December 2010, 40 families with 14 different disease causing mutations formed part of this programme.

The terminology surrounding this inherited cancer syndrome remains confusing. Most authors refer to proven germline mutation positive (i.e. loss of MMR gene expression or known MMR disease causing mutation) family members as having Lynch syndrome. The remaining individuals fulfilling the Amsterdam II criteria, but without detectable

mismatch match repair (MMR) gene mutations are classified as "Familial colorectal cancer syndrome"(11). The clinical behaviour of these two groups of inherited cancers is significantly different and will be discussed later. HNPCC is the term used originally to distinguish on clinical grounds, HNPCC from Familial Adenomatous Polyposis (FAP). It has fallen out of favour to some extent, but is still used to refer to Lynch syndrome related CRC and will be used in that regard in this text.

1.2 Diagnosis and Genetics

The diagnosis of HNPCC in the pre-genetic testing era was based on a set of clinical features formulated by the International Collaborative Group on HNPCC in 1991(12). The Amsterdam I criteria (Box 1) formulated at this meeting focussed only on inherited CRC. In recognition of the broader scope of inherited cancers in affected families, these diagnostic criteria were revised in 1999 (Amsterdam II criteria, Box 2)(13) to include the spectrum of inherited extracolonic tumours also associated with HNPCC.

Box 1: Amsterdam I criteria

At least 3 relatives with colorectal cancer (CRC) plus all of the following

- one relative should be a first degree relative of the other 2
- at least 2 successive generations should be affected
- at least 1 tumour should be diagnosed before the age of 50yrs

Box 2: Amsterdam II criteria

At least 3 relatives with colorectal cancer (CRC) or with a Lynch syndrome-associated cancer: cancer of the endometrium, small bowel, ureter or renal pelvis plus all of the following

- one relative should be a first degree relative of the other 2
- at least 2 successive generations should be affected
- at least 1 tumour should be diagnosed before the age of 50yrs
- Familial adenomatous polyposis should be excluded in CRC case

1.2.1 Mechanism of action:

HNPCC displays an autosomal dominant inheritance pattern. The genetic defect occurs in a set of genes that encode for proteins (enzymes) responsible for the correction of replication errors during somatic cell division. These enzymes of MMR(14)(1) genes either identify and replace transcription mistakes or assist in the induction of cell apoptosis if not correctable. Loss of this tumour suppressor ability plays a central role in CRC tumourgenesis in HNPCC/Lynch syndrome. By 1993 molecular genetics were able to identify the loci of the two most common germline mutations, MSH2 (mutS homologue 2) and MLH1 (mutL homologue 1) on chromosomes 2p and 3p respectively(15)(16). Subsequently further mutations have been identified. Currently MLH1 (50%), MSH2 (39%), MSH6 (7%) and PMS2/PMS1/MLH3 (4%)(17) comprise what are believed to be the causative mutations, with only the MLH1, MSH2, MSH6 and sometimes PMS2 routinely tested for in suspected HNPCC.

1.2.2 Detection of HNPCC

1.2.2.1 Microsatellite instability

In tumour DNA the loss of MMR genes manifest as microsatellite instability (MSI)(18). Microsatellites are predictable, multiple, usually noncoding sequences of mono – or dinucleotide repeats on either side of segments of functional DNA. This repetitive nature makes them highly susceptible to replication errors that lead to increased variation (i.e. instability) in their length, making microsatellites useful markers for diagnostic tests on CRC tumour tissue. An international standardised set of five (up to 10 in certain institutions) markers are used for MSI testing(19). Tumours are classified as MSI-high (MSI-H) if 2 or more (or >30%) of the markers test for instability, MSI-low (MSI-L) when 1 (or < 30%) and MSI-stable (MSI-S) if none show instability. MSI-H is found in more than 90% of HNPCC CRC tumours(19) . MSI-H is also reported in 10-15% of sporadic CRC secondary to hypermethalysation of both alleles of the MLH1 promotor during tumourgenesis, silencing their protein expression(20). The frequent presence of the V600E mutation of the BRAF proto-oncogene in sporadic CRC with

MSI-H can be used to exclude them from the HNPCC group. The use of MSI in population based screening of all CRC specimens has been shown to be positive in almost 20%(12,6% for only MSI-H) of cases, but only 2,2% of them had a detectable germline mutation(21). MSI testing therefore has a sensitivity of > 90%(22), but a low specificity of about 20% for identifying MMR gene abnormalities.

1.2.2.2 Immunohistochemistry:

Immunohistochemistry (IHC) techniques for detecting the loss of the specific MLH1, MSH2, MSH6 and PMS2 proteins in CRC tumours have been developed to improve on the sensitivity and specificity of MSI testing. Variable sensitivities and specificities for IHC have been reported in the literature, ranging from as high as 92.3% and 100%(23) respectively to a sensitivity as low as 48% in certain missense mutations of MLH1(24). The one advantage of IHC is that it provides a more focused confirmatory test for a germline mutation.

The Bethesda guidelines (Box 3) were developed in 1997 (revised 2004) to select patients who present with CRC for further MSI and/or IHC testing in order to increase the yield and reduce the cost of genetic testing of all CRC specimens(25). These guidelines were much broader in order to detect individuals with HNPCC that fell outside of Amsterdam II criteria. The sensitivity of the Bethesda guidelines versus the Amsterdam II criteria for germline mutations is 89% versus 40%(11)(26). The positive predictive value of the Bethesda guidelines compared to the Amsterdam criteria is 10-20% and 50% respectively. Even broader inclusion criteria for tumour MSI/IHC have been proposed(27). This will detect more mutations, but increase the overall cost.

1.2.2.3 Prognosis:

Patients with MSI-H(sporadic or inherited) CRC have been found to have a better overall long term prognosis and also may not benefit from the use of adjuvant 5-fluoro-uracil (5-FU) based chemotherapy regimens(28). This observation may add some motivation to the argument of testing all CRC tumours for MSI, with the added benefit of detecting an increased number of HNPCC individuals.

Box 3: Revised Bethesda criteria

Any of the following tumours should be tested for Microsatellite instability or Immunohistochemistry for miss match repair genes

- Colorectal cancer (CRC) diagnosed in a patient before age 50
- Presence of synchronous, metachronous colorectal or other Lynch syndrome-related tumours* regardless of age
- CRC with MSI-high histology diagnosed in a patient before age 60
- Patient with CRC and a first-degree relative with a Lynch syndrome-related tumour, with one of the cancers diagnosed before age 50
- Patient with CRC with 2 or more first- or second-degree relatives with a Lynch syndrome-related tumour, regardless of age

*Colorectal, endometrial, stomach, ovarian, pancreas, renal pelvis, biliary tract, brain and small bowel

None of the clinical or laboratory diagnostic guidelines or tools is 100% accurate in detecting all mutation positive patients. The Cancer Genetics study consortium (USA) has proposed a diagnostic algorithm to assist in this regard(29).

1.3 Cancer Risk

The lifetime risk of CRC in subjects that fulfil the Amsterdam II criteria varies between 60-85%(30). Higher (80-85%) lifetime risks were often quoted in past due to the selection bias towards high risk families in certain studies(22). Better understanding of the genetics of Lynch syndrome have shown that the individual cancer risk is influenced by gender, the presence of a germline mutation, the type of MMR gene abnormality and a family cancer history(29). MLH1 and MSH2 mutations have the highest lifetime CRC risk of 70%, a median onset of 44 years(31) and slight male predominance. This combination of characteristics makes MLH1 and MSH2 MMR gene abnormalities responsible for the so called "Classic" Lynch syndrome(31) . Mutations

of MSH6 and PMS2 produce a more "attenuated" form of Lynch syndrome with a mean age of onset of 55 years in males and 57 years in females(22). The cumulative lifetime risk for CRC in these males is not significantly different from the "Classic" Lynch Syndrome, but for MSH6 positive female subjects the risk is only 30%(22). The rest of the unique features of HNPCC are to some degree shared between all the MMR gene mutations. A 70% or greater incidence of colon cancer proximal to the splenic flexure(32) and an accelerated Adenoma-Carcinoma sequence of 2-3years (compared to 8-10 years in sporadic CRC) are found(33). There is also a propensity towards synchronous and metachronous CRC lesions(34). Familial colon cancer syndrome displays an even longer onset delay (mean age 60 years), a lower total risk (standard incidence ratio of 2.3 vs. 6.1 for CRC) and no increased risk for extracolonic cancers(35). On histology the CRC associated with HNPCC most often shows poor differentiation, signet or muscinous cell type, lymphocyte infiltrates and a medullary growth pattern(36). These features in any CRC specimen should prompt the pathologist to further investigate for HNPCC.

A range of extracolonic cancers are associated with Lynch syndrome. Endometrial cancer is the most prevalent at a 30-70% lifetime risk at 70 years of age with MSH6 mutation positive females at 70% having the highest risk compared to other MMR mutations(22). In decreasing order of risk ovarian (3-13%), gastric (2-13%), urinary tract (1-12%), small bowel especially duodenum (4-7%), brain tumours, billiary tract and pancreas cancers are all closely associated with Lynch syndrome(11) .

1.4 Colorectal Cancer Screening

The high risk of developing CRC in Lynch syndrome individuals compared to the general population justifies a more intense programme than currently used for population based CRC screening. The International Collaborative Group on hereditary nonpolyposis colorectal cancer (ICG-HNPCC) proposed 2 yearly intervals between full colonoscopies starting at 20-25 years and to be continued lifelong or until medically

unfit for surgery(12). This protocol tries to encompass the features of rapid progression from adenomatous polyps and the high percentage of proximal cancers so unique to HNPCC. The later presentation of CRC in known MSH6 mutation positive subjects and Familial Colorectal Cancer syndrome has prompted some authors to suggest a screening programme with a later onset, but this is not yet universally accepted(35)(22). The programme used by the GSH Colorectal Unit involves surveillance colonoscopy every two years from 16-30 years of age and yearly there after(9). Surveillance colonoscopies have been shown to improve disease free and overall survival in HNPCC families through removal of adenomatous polyps. A Finnish study conducted over 15 years in 22 high risk families (Amsterdam II criteria positive) demonstrated a 62% reduction in CRC, 56% reduction if only mutation positive individuals were considered, in screened compared to unscreened subjects from these families(37). No CRC related deaths were reported in the surveillance group versus 8% in the control group in the same families. The tumours detected were either Dukes A-B CRC (25%) or adenomatous polyps (75%)(38)(39). A 70% reduction in the standardised mortality ratio was shown over time after the introduction of surveillance colonoscopies in the Dutch HNPCC registry(40) . South African data on MLH1 mutation positive individuals followed for a mean of 5 years, report the development of CRC in 11% of subjects on surveillance compared to 27% in the no surveillance group. Similar to the Finnish data, the cancers detected in the surveillance group were of a much earlier stage. The median CRC free survival from birth improved significantly for the subjects on surveillance (73 vs. 47 years; P=0.0089)(41).

The more rapid Adenoma-Carcinoma sequence in HNPCC combined with colonoscopy miss rates for tumours and the lack of screening compliance can lead to the development of interval CRC on surveillance. A Dutch study estimated the CRC risk on surveillance over 10 years to be between 10-15%(42). In Finland, where for many years a 3 year screening interval between colonoscopies was standard practice for those on surveillance, the cumulative risk between 20 and 60 years of age was 34.6% in men and 22.1% in females(43). The high incidence of CRC proximal to splenic flexure (up to 70%) makes a complete colonoscopy essential in HNPCC surveillance. Complete colonoscopies, which entail reaching the caecum, are accomplished in 97% of cases

done by experienced endoscopists. This figure can be as low as 54% if self-trained(44). A 96% completion rate is achieved by the UCT colonoscopy unit in GSH as well as on community outreach colonoscopies(45). The adenoma miss rate of same day performed tandem colonoscopies varies between 15-24% for lesion less than 1 cm and 0-6% for larger adenomas(46)(47). The use of chromo-endoscopy, spraying colonic epithelium with indigo carmine or methylene blue during colonoscopy, to increase detection of small subtler adenomas against a background of normal colonic mucosa has been suggested(48). Up to 25% of high risk CRC subjects deviate significantly from proposed surveillance regimens(49) . Surveillance colonoscopies improve overall and cancer free survival, but the above factors show it not to be fail safe.

Virtual colonography, via computer tomography (CT) or magnetic resonance imaging (MRI), makes use of new technology to avoid the morbidity associated with the invasive nature of repeated colonoscopies. CT colonography has been found comparable to standard colonoscopy in the detection of CRC, but superior in completion rate (96.7 vs. 86%) and inferior in identifying small adenomas (only 46% of adenomas < 5mm found on colonoscopy)(50). CT also has the disadvantage of repeated radiation exposure in patients requiring long term surveillance. MRI colonography in mutation positive HNPCC subjects detected all lesions larger than 1cm, but none smaller(51). Both investigations need to be followed by a colonoscopy with polypectomy in cases with detected lesions.

1.5 Surgical Management Options

The American Society of Colon and Rectal Surgeons recommends for HNPCC individuals with more than one advanced adenoma (larger than 1 cm, villous architecture or high grade dysplasia) or cancer a total colectomy and ileorectal anastomosis(with lifelong rectal surveillance) or a proctocolectomy and ileo-anal pouch for rectal lesions(52) . Following surgery there remains a 12% risk of developing rectal cancer over 12 years; requiring ongoing, although easier, surveillance(53). Segmental resections are discouraged due to the high risk of synchronous (18%) and metachronous disease (45% over 10 years)(34). Limited resections have been

associated with a higher risk of a second CRC(54). Data from the colorectal unit in GSH reported a 20% 5 year and 41% 15year risk of metachronous lesions in their population of HNPCC patients. CRC related deaths occurred in 33% of the segmental resection group and 10% in those undergoing total colectomy(55). The survival benefit in years for extended colectomy compared to a limited resection is 2.3 years(56). Sygnal et al used a mathematical model to predict that a total colectomy done prophylactically at age 25 has the longest survival benefit. No increase in life expectancy was found if the surgery was done at detection of CRC or adenomatous polyps compared to surveillance in HNPCC subjects(57). Quality of life considerations are important in comparing prophylactic surgical strategies to ongoing surveillance in HNPCC subjects with no or only premalignant lesions (adenomatous polyps). The quality of life post total colectomy has only been studied in FAP and concluded that the procedure was safe with minimal disturbance in stool habits(58). The median age of this study group was 28 years versus 44 years(31) in most HNPCC individuals receiving a total colectomy. Even this much younger group had on average 4.2 stools per day that may be worse in older people with a poorer sphincter function. The up to 9.5% incidence in hospital admission for adhesive small bowel obstruction post open total colectomy further complicates the decision making regarding prophylactic surgery in a remote population(59). With no clear guidelines(60), the timing and type of procedure should be based upon patient factors including age, co-morbidity, sphincter function and compliance with a surveillance programme(61).

1.6 Conclusion

The long-term strategy for an HNPCC individual remains unclear. Surveillance colonoscopy with polypectomy of adenomas has been shown to decrease mortality and prolong cancer free survival(38)(41). Mathematical models demonstrated a survival benefit of early total colectomy over ongoing surveillance(57). This debate is further fuelled by the absence of clear reproducible pathology criteria to distinguish low from high grade dysplasia in colonic adenomatous polyps, leading to inter observer variability(62). This complicates surgical decision making based on the degree

of dysplasia reported on adenomatous polyps found during surveillance colonoscopy(52).

A large percentage of the HNPCC population being investigated by the GSH Colorectal Unit and the Department of Human Genetics at UCT is resident in remote areas of the Northern Cape(8)(63)(10)(45). These resource poor communities pose other challenges above and beyond the pure clinical ones stated previously that influences decision making regarding surveillance versus surgery when considering the individual with benign adenomatous polyps and HNPCC. Limited access to healthcare (especially specialists), lack of transport, poor education and general lower socio-economic status adds to this burden. The research into this isolated population of HNPCC is unique in the literature.

The purpose of this study therefore is to document and review the natural history of adenomatous polyps in our HNPCC cohort combined with the outcomes of our current surgical or endoscopic management of these patients. Analysis of this data will add to the growing body of evidence in relation to this disease with specific reference to its South African context. This will assist in adapting existing management protocols for application in our setting.

CHAPTER TWO: Aim and Objectives

2.1 Aim

The aim of this study was to determine the colorectal cancer free survival of individuals with Lynch Syndrome and found to have benign adenomatous polyps on routine surveillance colonoscopy.

2.2 Objectives

Primary Objective: To compare the cancer free survival of biopsy proven benign adenomatous polyps in HNPCC patients receiving colonic resection with those on continued surveillance colonoscopy and endoscopic polyp removal.

Secondary Objectives:

A. Surgical group:

1. To determine a relationship between the grade of dysplasia in the adenomatous polyps and the identification of an unexpected cancer in the resected specimen.
2. To determine the relationship between the number of adenomatous polyps and the risk of an unexpected cancer in the resected specimen.
3. To determine the relationship between the anatomical location of the polyp and the risk of an unexpected cancer in the resected specimen.
4. To determine the relationship between the size of the adenomatous polyp and the risk of an unsuspected cancer in the resected specimen.

B. Surveillance group:

1. To determine the time span to the development of colon cancer on continued colonoscopic surveillance.

CHAPTER THREE: Methodology

3.1 Study design:

This study is a retrospective review of a prospectively collected patient cohort from the Groote Schuur Colorectal Unit and UCT Department of Human Genetic's HNPCC registry. All patients with a known germline mutation of MLH1 or MSH2 underwent surveillance colonoscopies. The protocol at the GSH Colorectal Unit is 2-yearly colonoscopies from 16-30 years and yearly thereafter(9) . The patients entered the study after an index colonoscopy detected a benign adenomatous polyp(s). There was no protocol dictating management when adenomatous polyps were identified. All polyps were removed at colonoscopy. Further management consisted of both colectomy and ileorectal anastomosis or continued surveillance. The decision was at the discretion of the treating physician and/or the choice of the patient. The surgical specimens were evaluated for unexpected cancer in what was preoperatively presumed to be a resection for benign disease. The surveillance group continued regular colonoscopies with removal of all further polyps. A 96% completion rate is achieved by the UCT colonoscopy unit in GSH as well as on community outreach colonoscopies(45) , and all endoscopists have undergone supervised training.

3.2 Study population:

All patients known with the MLH1 and MSH2 HNPCC mutation in the UCT Registry up to 31 December 2010.

3.3 Sample size and method:

All mutation positive HNPCC individuals found to have adenomatous polyps on surveillance colonoscopy. Sample size was limited by the number of patients in the registry.

3.4 Inclusion criteria:

HNPCC mutation positive individuals with histologically proven benign adenomatous polyps removed during surveillance colonoscopy.

3.5 Exclusion criteria:

1. Biopsy proven colon cancer on first surveillance colonoscopy.
2. Any form of previous colorectal surgery for malignant disease.
3. History of colorectal cancer.
4. < 18 years of age

3.6 Outcome variables:

1. Detection of unexpected cancer on resected colon specimen.
2. Development of cancer on surveillance colonoscopy.

3.7 Determinant variables:

1. Gender
2. Age at first colonoscopy that showed adenomatous polyp.
3. Specific mismatch repair (MMR) gene mutation.

- Distinguish between MLH1 and MSH2 only via genetic testing.
- This excludes other forms of MMR gene mutations and subjects with Familial Colorectal cancer syndrome.

4. Grade of polyps on biopsy taken at colonoscopy
    - The pathological specimens are histologically classified as high or low grade dysplasia via light microscopy.
    - All histology reports are reviewed by a qualified specialist anatomical pathologist.

5. Number of polyps on colonoscopy

6. Anatomical location of polyps on colonoscopy
    - The anatomical location as visualised by endoscopist is divided into ascending colon, transverse colon, descending colon, sigmoid colon and rectum.

7. Size of polyps found on colonoscopy
    - Size estimated by endoscopist at colonoscopy in millimeters.
    - For comparison polyps divided into less than 10mm and 10mm or greater.
    - Where the report did not record the size of the polyp it was captured in the study database as "not recorded".

8. Histology of any resected specimens.

- Reporting of malignancy according to the American Joint Committee on Cancer (AJCC) 2010 TNM (tumour, node, metastasis)-classification.
- The position of any detected cancer to be correlated with preceding polyp removal/ biopsy at endoscopy.

9. Duration between surveillance colonoscopies in years.

10. Duration from index colonoscopy to detection of cancer on biopsy while on surveillance.

3.8 Ethical considerations:

Patient information was collected in such a way as to protect confidentiality throughout the study. Numeric codes were assigned to individuals to maintain anonymity. All subjects received formal counselling and signed written consent for genetic testing and surveillance colonoscopy as part of a larger ethics approved study by the UCT Department of Genetics and Colorectal Surgery Unit (HREC 474/2011). The study adhered to the guidelines of the 2008 Helsinki declaration(64).

3.9 Statistical analysis:

Measures of central tendency and spread where calculated as the mean with standard deviation for normally distributed data and median with interquartile range for non-normally distributed data. Hypothesis tests were performed on numeric data using the unpaired T-test and on categorical data using the Chi-square test. If the assumptions for the Chi-square test were not met the Fishers-exact test was used instead. All hypothesis tests were two-sided with the level of significance set at 0.05 after Bonferroni adjustment for multiple comparisons. All statistical analysis was performed using R version 2.13.1 (The R Foundation for Statistical Computing).

3.10 Cost:

All costs incurred during this study were funded by the investigator.

CHAPTER FOUR: Results

4.1 Description of cohort

The UCT Department of Human Genetics and Colorectal Surgery Unit HNPCC registry identified 318 individuals with known disease causing mutations (MLH1 and MSH2) from 36 families. Fifty one subjects (Diagram 1) entered the study between 1986 up to and including December 2010 after a surveillance (index) colonoscopy detected a histologically proven adenomatous polyp. Twenty four males (47.1%) and 27 females (52.9%) with a mean age of 42 years (SD 10, Range 23-73) met the entry criteria. The MLH1 and MSH2 mutations were identified in 46 (90.2%) and 5 (9.8%) of the 51 patients respectively (Table 1).

The 51 subjects underwent a total of 95 colonoscopies from 1986 to December 2010, during a total of 74 years of patient follow-up. The median number of colonoscopies per person was 1 (range 1-6), with 30 (59%) only ever undergoing a single colonoscopy.

Seventy six polyps were detected in total. Fifty six colonoscopies identified 1 adenomatous polyp each and 10 colonoscopies identified 2 polyps each. The surgical group yielded 36 polyps and the surveillance group 40 polyps. The median number of adenomatous polyps detected per patient was 1 (range 1-5, IQR 1-2).

Of the 76 polyps identified 27 were positioned in the ascending colon, 28 in the transverse colon, 2 in the descending colon, 9 in the sigmoid colon and 10 in the rectum. Seventy two percent of all the polyps were detected proximal to the descending colon.

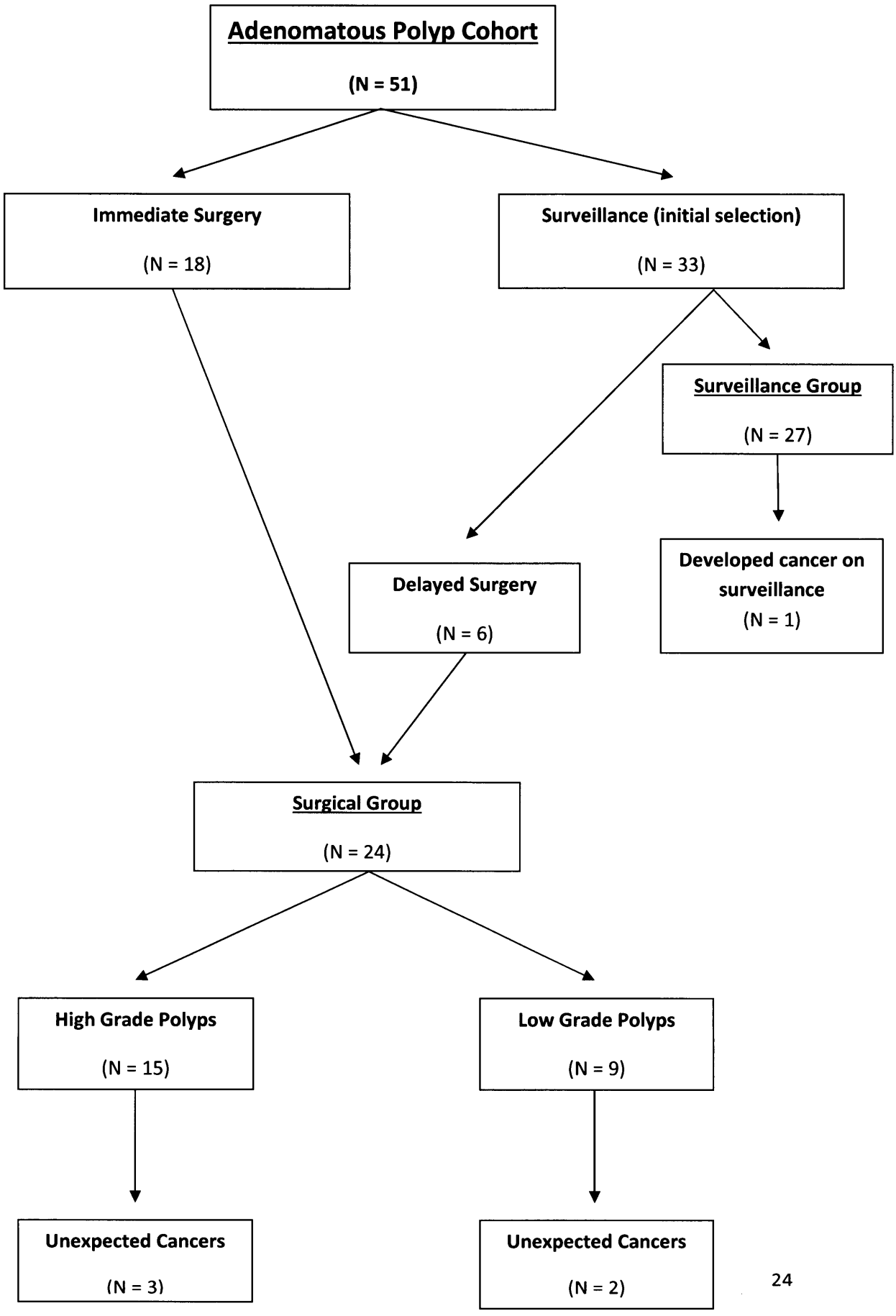
Fifty one of the 76 identified polyps had size documented at colonoscopy. Forty polyps were smaller than 10mm and 11 polyps (in 10 patients) were 10mm or larger according to the estimation of the endoscopist. On histology 52 of the 76 adenomatous polyps were graded as low grade and 24 as high grade. The 24 high grade polyps were detected in 20 patients.

Table 1: Demographic and genetic characteristics of the cohort

	Total (N = 51)	**Cancer (N = 6)**	**No Cancer (N = 45)**	**P-value**
Mean Age * in years (SD)	42 (10)	50 (20)	41 (8)	0.05
Gender				0.4
Male (%)	24 (47.1)	4(66.7)	20(44.4)	
Female (%)	27 (52.9)	2(33.3)	25(55.6)	
MMR gene mutation				0.5
MLH1 (%)	46(90.2)	5(83.3)	41(91.1)	
MSH2 (%)	5(9.8)	1(16.7)	4(8.9)	

*at index colonoscopy

Diagram 1


Adenomatous Polyp Cohort
(N = 51)
Immediate Surgery
(N = 18)
Surveillance (initial selection)
(N = 33)
Surveillance Group
(N = 27)
Developed cancer on surveillance
(N = 1)
Delayed Surgery
(N = 6)
Surgical Group
(N = 24)
High Grade Polyps
(N = 15)
Low Grade Polyps
(N = 9)
Unexpected Cancers
(N = 3)
Unexpected Cancers
(N = 2)

4.2 Surgical group

Twenty four patients underwent elective surgical resection of the colon for what was preoperatively expected to be for benign disease (Table 2). Eighteen had surgery on detection of an adenomatous polyp on the first available elective list (Immediate surgery), while a further 6 had at least one subsequent surveillance colonoscopy before the decision to proceed to resection was made (Delayed surgery).

The age, gender, MMR gene mutation subtype, number and location of the polyps was not statistically different from the group on continued surveillance (Table 3). All the patients (10 in total) with polyps with a documented size at colonoscopy of 10mm or more received surgical resection. Patients with high grade polyps at any time during surveillance proceeded to surgery in 16 of 20 cases. Fifteen patients (62.5%) had high grade polyps in the colonoscopy directly preceding surgery and nine (37.5%) of the surgical patients had low grade polyps. In the surgical group size equal or greater than 10mm and high grade polyp percentage were the only variables reaching statistical significance compared to the surveillance group (both $p<0.001$).

Size of 10mm or larger and/or high grade polyps combined were documented in 17 (70.8%) of the 24 patients in the surgical group at the colonoscopy before surgical resection. Eleven (45.8%) patients had no identifiable abnormalities (no polyps or malignancy) on final histology of the colectomy specimen. Five unexpected cancers were discovered in the 24 resected specimens. Unexpected colorectal malignancies did not occur more often in patients with high (20%) compared to low (22%) grade polyps ($p = 0.6$).

Table 2: Surgical group

	Total (N = 24)	**High Grade (N=15)**	**Low Grade (N=9)**
Immediate surgery	18	12	6
Delayed surgery	6	3	3
Unexpected cancer	5	3(20%)	2(22%)

4.3 Surveillance group

Twenty seven patients selected ongoing surveillance. One proceeded to surgical resection after developing colorectal cancer while on surveillance. Twelve (44.4%) of the 27 patients on surveillance received only a single index colonoscopy, 7 had 2 colonoscopies, 2 had 3 colonoscopies, 4 had 4 colonoscopies and 2 patients had 5 and 6 surveillance colonoscopies respectively. Of the 12 patients with a single colonoscopy only 2 were lost to follow-up, while the remainder (10) were awaiting their next surveillance colonoscopy beyond December 2010.

No study subject with a polyp identified to be equal to or larger than 10mm in size at colonoscopy received non-operative care (Table 3).

Four of 20 patients with a high grade adenomatous polyp identified at any time were continued on ongoing surveillance and polypectomy. Two of these patients showed resolution of the high grade polyps on subsequent colonoscopies, while the third was lost to follow-up.

The fourth was the only patient, as mentioned above, to develop colorectal cancer while on surveillance. The cancer was detected in a 67 year old female at the patient's fourth colonoscopy over a period of 6 years. The malignancy was found 1 year after a routine surveillance colonoscopy detected a HG polyp at the same site. This sigmoid tumour was a T2 N1 adenocarcinoma.

Table 3: Surgical versus Surveillance group comparison

	Surgical group (N=24)	Surveillance group (N=27)	P-value
Mean Age* in years (SD)	42 (11)	42 (10)	0.7
Gender			0.5
Male (%)	13(54.2)	11(40.8)	
Female (%)	11(45.8)	16(59.2)	
MMR gene mutation			0.4
MLH1 (%)	23(95.8)	23(85.2)	
MSH2 (%)	1(4.2)	4(14.8)	
Polyp Grade			<0.001#
LG Polyps only (%)	8(33.3)	23(85.2)	
At least 1 HG Polyp (%)	16(66.7)	4(14.8)	
Polyp Size			<0.001#
All Polyps <10mm only (%)	7(29.2)	23(85.2)	
At least 1 polyp ≥10mm (%)	10(41.6)	0(0)	
Never documented (%)	7(29.2)	4(14.8)	

*at index colonoscopy; # = corrected for multiple comparisons; HG = high grade; LG = low grade; SD = standard deviation

4.4 Colorectal cancers

The cohort yielded 6 cancers in total over 74 patient follow-up years (Table 4). Five patients were found to have unexpected cancers (3 receiving immediate and 2 delayed surgery) and one developed cancer while on surveillance. The mean age of this cancer subgroup was 50 years (SD 20, range 29-72), compared to 42 years of the whole cohort (Table 1). All the unexpected cancers were at the same site as the preceding endoscopic polyp removal/biopsy that showed benign disease. No synchronous cancers were detected. Four patients had high grade polyps in the surveillance

colonoscopy immediately prior to cancer detection compared to 2 with low grade polyps in the most recent colonoscopy. One of these patients with a low grade polyp had a high grade polyp identified in a colonoscopy 8 years previously at the same site as the cancer and was continued on surveillance at that time (Table 4).

Table 4: Cases of Colorectal Cancer

	Position	Polyp Grade	Polyp Size	Stage of cancer
1	Transverse colon	Low	Not recorded	T2N1 (1/8 nodes)
2	Transverse colon	High	>= 10mm	T1N0
3	Ascending colon	High	>= 10mm	T2N0
4	Ascending colon	Low	Not recorded	T2N0
5	Ascending colon	High	Not recorded	T2N1 (1/28 nodes)
6	Sigmoid colon*	High	Not recorded	T2N1

*developed cancer on surveillance

These six patients were significantly different to the non-cancer patients in the cohort with regards to age (p=0.05, not corrected for multiple comparisons, Table 1) and proportion of high grade polyps (p=0.05, corrected for multiple comparisons, Table 5). No significant difference was found regarding gender, mutation subtype, number, position or size of polyps to distinguish those that developed cancer from those that remained cancer free at the end of the observation period.

All the cancers were early (T1-2) and only 2 of the six patients had node positive disease. The two patients receiving delayed surgical resection as well as the patient that developed cancer on surveillance each experienced a six year time lapse in between index colonoscopy and detection of colorectal cancer.

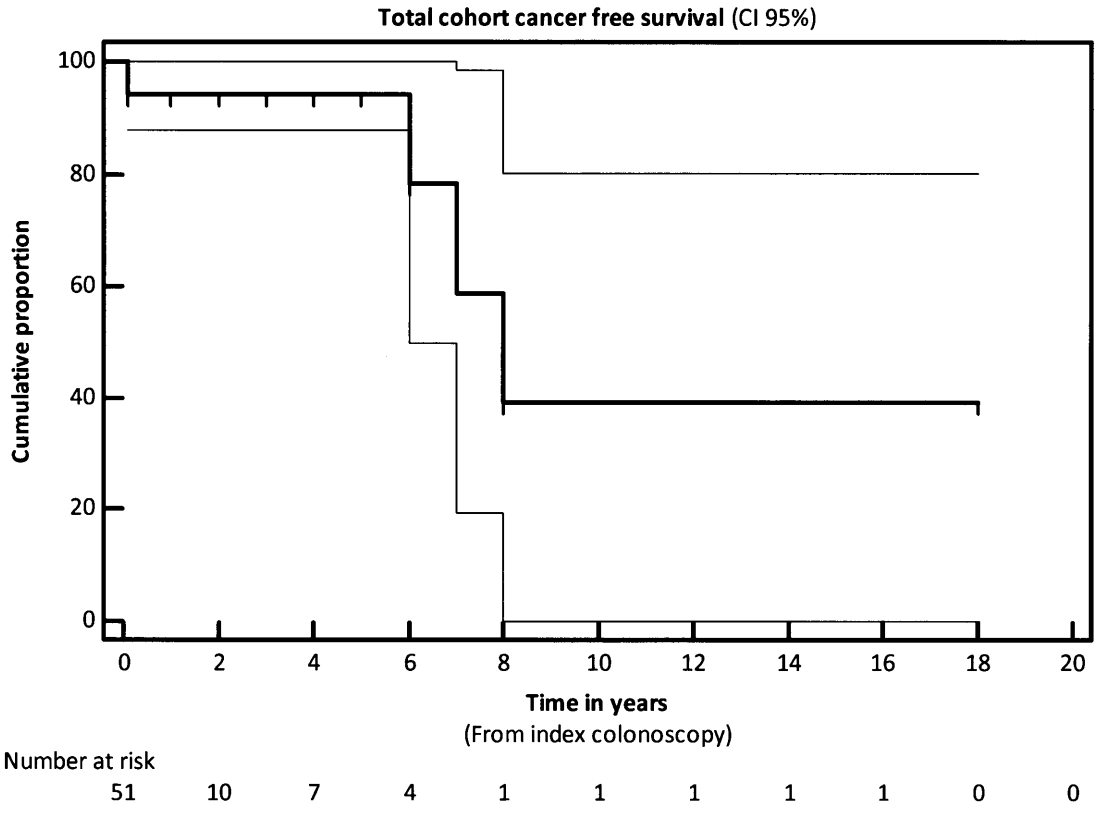
Table 5: Comparison of Colorectal Cancer versus Cancer Free survivors in the Cohort

	Total group (N=51)	Cancer (N=6)	No Cancer (N=45)	P-value
Polyp Grade				0.05#
LG polyps only (%)	31 (62)	1(16.7)	30(66.7)	
At least 1 HG polyp (%)	20(38)	5(83.3)	15(33.3)	
Polyp Size				0.1#
All Polyps <10mm (%)	30(58.8)	0(0)	30(66.7)	
At least 1 polyp ≥10mm (%)	10(19.6)	2(33.3)	8(17.8)	
Never documented (%)	11(21.6)	4(66.7)	7(15.5)	

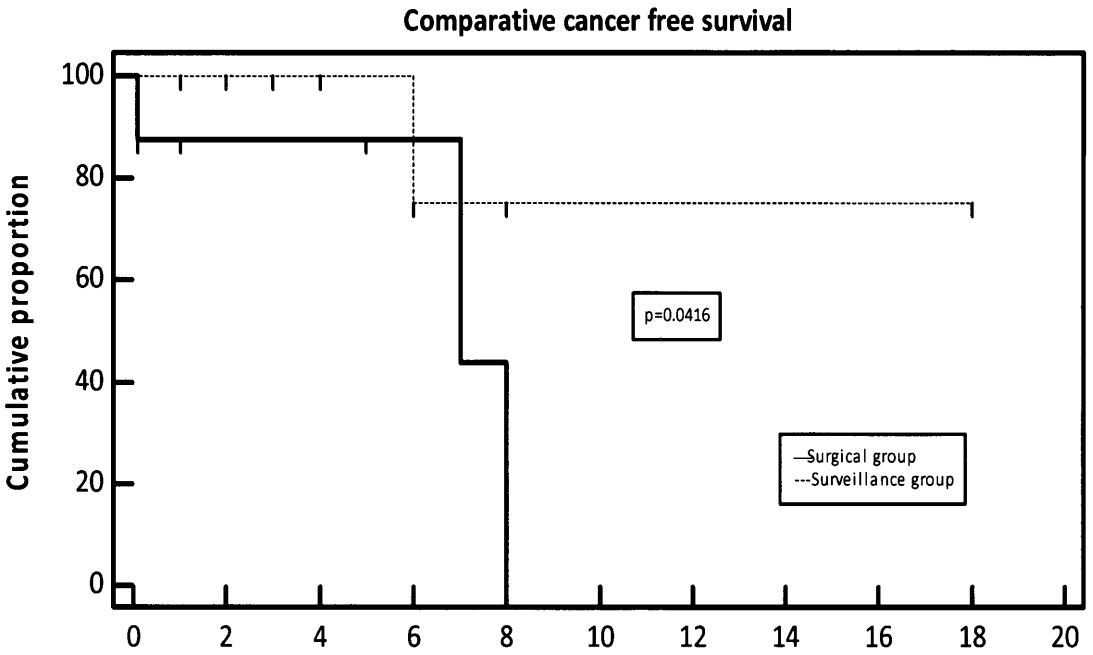
= corrected for multiple comparisons; HG = high grade; LG = low grade

The median cancer free survival from the index colonoscopy for the total cohort is 8 years (Graph 1). The comparative Kaplan Meier estimate of cancer free survival between surgical and surveillance groups reached statistical significance (p=0.04) in favour of surveillance (Graph 2). The median colorectal cancer free survival from index colonoscopy is 7 years in the surgical group and not reached in the surveillance group. The surgical group is right censored to zero within 8 years and explains the steep drop off on graph 2.

Graph 1: Kaplan Meier estimate of total cohort cancer free survival



Graph 2: Comparative Kaplan Meier estimate of Surveillance and Surgical group



Number at risk

Group: Surgical group										
24	3	3	2	0	0	0	0	0	0	0
Group: Surveillance group										
27	7	4	2	1	1	1	1	1	0	0

CHAPTER FIVE: Discussion

HNPCC is the most common inherited colorectal cancer and is responsible for 2-5% of the total colorectal cancer burden(3)(4)(5). The resource-limited origin of the GSH Colorectal Department and the UCT Department of Human genetics HNPCC registry is unique in the literature. Fifty one known mutation positive HNPCC patients entered this study when benign adenomatous polyp(s) was detected on routine surveillance colonoscopy. The composition of this group is comparable to similar cohorts in Europe and North America regarding patient age, gender and polyp position(31)(32). The MMR gene mutation distribution favouring MLH1 (90.2%) has been described previously in this population(41).

The decision to proceed to surgical resection was taken in 70.8% in accordance with guidelines published by the American Society of Colon and Rectal surgeons (i.e. adenomatous polyps 10mm or larger, high grade dysplasia or villous architecture)(52). This finding was supported by size (equal or greater than 10mm) and polyp grade (High grade) that reached comparative statistical significance ($p < 0.001$) in favour of the surgical group. No residual evidence of an adenomatous polyp was detected in 42.5% of final colectomy specimens demonstrating complete removal by preceding endoscopic polypectomy. The remote nature of our HNPCC population and potential of poor follow-up could have favoured surgery above ongoing surveillance in these patients.

Unexpected cancers were found in equal proportion in patients with high and low grade polyps in the colonoscopy directly preceding surgical resection (20% and 22% respectively, $p=0.6$). Unexpected colorectal cancer at surgery that preoperatively was thought to be for benign disease in HNPCC has not been documented in the literature. In this study 1 out of 5 patients in the surgical group harboured a malignancy in a biopsy proven benign adenomatous polyp. The conclusions that could be drawn from this are limited by the small numbers and paucity of information regarding the motivation for surgery in each individual patient. Clinical suspicion of malignancy by the treating surgeon could have overridden final polyp histology and deemed the biopsy to be non-representative. Despite the lack of statistical significance ($p=0.1$), due

to the poor documentation of polyp size, the observation of a minimum of 33% of patients with unexpected CRC having polyps > 10mm compared to 17.8% of patients without CRC is an important clinical observation.

GSH Colorectal Unit performs biannual colonoscopies from 16-30 years and yearly there after(9) . This combined with a sponsored rural mobile colonoscopy outreach program aims to increase compliance of surveillance equal to the published norm. Only 2 participants of the surveillance group were deemed to be lost to follow-up. Most recent guidelines suggest two-yearly colonoscopies from 20-25 years of age(12)(11). Previously published data from this unit showed a 96% completion rate(45) . Only one patient from this cohort developed cancer while on surveillance colonoscopy and polypectomy. This is in keeping with the high quality endoscopy service offered. The limited follow-up of the surveillance group is demonstrated by 10 (37%) of the 27 patients still awaiting their second colonoscopy. Similar prevalence (20%, 1/5 for all grades of polyps) of malignancy hidden in the benign polyps was not seen in the surveillance group compared to the surgical group illustrated by the low rate of transformation to overt malignancy. This suggests that other factors influenced surgical decision making and accounted for the high rate of unexpected cancer in the surgical group.

Stupart et al have shown a significant cancer free survival benefit in all MLH1 mutation positive patients on surveillance versus no surveillance from the same population as this study(41). Dutch(42), Finnish(43) and our own published data looked at surveillance and cancer free survival in the HNPCC population as a whole and did not specifically focus like this study on the subgroup with known adenomatous polyps .

The aim of this study was to determine the cancer free survival of these mutation positive individuals after detection of a benign adenomatous colorectal polyp. The median cancer free survival for the cohort from index colonoscopy was found to be 8 years. The primary outcome of cancer free survival was significantly less for the surgical compared to the surveillance group. This higher rate of unexpected cancer in the surgical group (1 out of 5 selected for surgery) seems to be confounded by the indication for the surgery. The surgical group had significantly more high grade polyps

($p<0.001$) and significantly more large polyps ($P<0.001$) than the surveillance group suggesting that the clinical decision to opt for surgery as opposed to continued surveillance was based on an appropriately high index of clinical suspicion of potential cancer. Ignoring this possible selection bias towards surgery this study still shows that more than 1 out of 10 patients (6 cancers in the total of 51 patients) diagnosed with a benign adenomatous polyp will go on to develop a colorectal cancer over a mean period of 8 years from detection of benign adenomatous polyp.

As would be expected, following the natural history of HNPCC and CRC the mean age of the cancer group was significantly older than the non-cancer group (51 compared to 40 years); however there was no difference in those that received surgical management versus surveillance. Considering that almost half of the patients on surveillance colonoscopy have not yet been in follow-up long enough to have received a second colonoscopy; the continued follow-up of this cohort over-time as they age has the potential to continue contributing valuable observational evidence in the absence of a randomized controlled trial as to the most suitable management strategy for this population of HNPCC/Lynch Syndrome patients.

CHAPTER SIX: Conclusion

A large percentage of the GSH colorectal unit's HNPCC population is resident in remote areas of the Northern Cape. This cohort showed a good level of compliance to surveillance colonoscopy after adenomatous polyp detection in spite of limited access to medical care. Data, with limitations, from this study is also in support for possible earlier surgical intervention with equal proportion of high and low grade polyps leading to an unexpected colorectal cancer. The significant data is still in support of high grade polyps and size of 10mm or greater to be followed by total colectomy and ileo-rectal anastomosis. Our HNPCC population live in poor communities with often inadequate sanitation services that need to be considered with the long term morbidity of a total colectomy.

More data is still needed to guide our decision making in regard to surgery versus continued surveillance on detection of a colorectal adenomatous polyp. Until then the management of patients with HNPPC/Lynch Syndrome should be conducted by a multidisciplinary team consisting of colorectal surgeons, gastroenterologists, geneticists and social workers in consultation with a well informed and properly counselled patient.

CHAPTER SEVEN: References

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CHAPTER EIGHT: Appendices

8.1 Abstract

CANCER FREE SURVIVAL IN MUTATION POSITIVE HNPCC INDIVIDUALS WITH COLORECTAL ADENOMATOUS POLYPS IDENTIFIED ON SURVEILLANCE COLONOSCOPY

Investigator: Dr Oostewalt Swart

Supervisor: Prof PA Goldberg

Introduction:

HNPCC (hereditary nonpolyposis colorectal cancer) is the most common inherited colorectal cancer (CRC) and is responsible for 2-5% of the total CRC burden. The management of a histologically benign adenomatous polyp detected on surveillance colonoscopy remains unresolved.

Aim:

The aim of this study was to determine the cancer free survival of individuals indentified with HNPCC via genetic testing and found to have benign adenomatous polyps on routine surveillance colonoscopy

Methodology:

This study was a retrospective review of a patient cohort from the Groote Schuur Colorectal Unit and UCT Department of Genetic's HNPCC registry up to December 2010. The decision on surgery or continued surveillance after polyp detection was at the discretion of the treating physician and/or the choice of the patient. The surgical group were evaluated for unexpected cancer in the surgical specimens. The surveillance group continued regular colonoscopies, with polyp removal, to detect/exclude transformation to cancer.

Results:

In the surgical group size equal or greater than 10mm and high grade polyp percentage were the only variables reaching statistical significance compared to the

surveillance group (both $p<0.001$). Five unexpected cancers were discovered in the 24 resected specimens. Unexpected colorectal malignancies did not occur more often in patients with high (20%) compared to low (22%) grade polyps ($p = 0.6$). The median cancer free survival from the index colonoscopy for the total cohort is 8 years. The comparative Kaplan Meier estimate of cancer free survival between surgical and surveillance groups reached statistical significance ($p=0.0416$) in favour of surveillance.

Conclusion:

Data, with limitations, from this study supports possible earlier surgical intervention with equal proportion of high and low grade polyps leading to an unexpected colorectal cancer.

8.2 Ethics Approval

UNIVERSITY OF CAPE TOWN

Department of Surgery

Departmental Research Committee
Professor Anwar Suleman Mall
J-45 Room Old Main Building, Groote Schuur Hospital,
Observatory 7925, South Africa
Tel (021) 406 6168/6232/6227 **Fax** (021) 448 6461
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28th February 2011

Dr O Swart
Department of Surgery
Division of Cardiothoracic Surgery
Groote Schuur Hospital
University of Cape Town

Dear Dr Swart

RE: PROJECT 2011/015

PROJECT TITLE: Cancer free survival in mutation positive HNPCC individuals with Colorectal Adenomatous Polyps indentified on surveillance colonoscopy

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

PROFESSOR ANWAR S MALL
CHAIRMAN: RESEARCH COMMITTEE

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Ms S Ariefdien - Tel: [021]4066492 • Fax: [021]4066411
email: sumayah.ariefdien@uct.ac.za

14 October 2011

HREC REF: 474/2011

Dr O Swart,
General Surgery
Department of Medicine
J-floor
OMB

CC. Prof P Goldberg
Surgical Gastroenterology unit

Dear Dr Swart,

PROJECT TITLE: CANCER FREE SURVIVAL IN MUTATION POSITIVE HNPCC INDIVIDUALS WITH COLERECTAL ADENOMATOUS POLYPS IDENTIFIED ON SURVEILLANCE COLONOSCOPY

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study

Approval is granted until 30 October 2012

Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file (FHS010).

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

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS

Federal Wide Assurance Number: FWA00001637
Institutional Review Board (IRB) number: IRB0000 1938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

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	30-10-2013
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	2/10/2012

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	02 October 2012		
HREC REF Number	474/2011	Current Ethics Approval was granted until	30 October 2012
Protocol title	CANCER FREE SURVIVAL IN MUTATION POSITIVE HNPCC INDIVIDUALS WITH COLORECTAL ADENOMATOUS POLYPS IDENTIFIED ON SURVEILLANCE COLONOSCOPY		
Principal Investigator	Dr Oostewalt Swart		
Department / Office Internal Mail Address	Department of Surgery/ Colorectal Surgery Unit		
1.1 Does this protocol receive US Federal funding?		☐ Yes	× No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
×	Data collection is complete, data analysis only

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		51
Total number of records or specimens collected, reviewed or stored since last progress report		N/A
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	× Yes	☐ No

4. Signature

Signature of PI		Date	02 October 2012
Signature of Supervisor (if PI is a student)		Date	

8.3 Research Proposal

CANCER FREE SURVIVAL IN MUTATION POSITIVE HNPCC INDIVIDUALS WITH COLORECTAL ADENOMATOUS POLYPS IDENTIFIED ON SURVEILLANCE COLONOSCOPY

INVESTIGATOR: Dr Oostewalt Swart

SUPERVISOR: Prof Paul Goldberg

LITERATURE REVIEW:

Hereditary nonpolyposis colorectal cancer (HNPCC) accounts for 3-5% of all colorectal cancers in the developed world.[1,2] It is an autosomal dominant disease with an inherited germ line mutation of mismatch repair (MMR) genes[3,4]: MLH1(50%), MSH2(39%), MSH6(7%) and PMS1/PMS2/MLH3(5%)[5]. This leads to DNA replication errors if followed by a subsequent somatic mutation of the remaining normal MMR allele. HNPCC mutation positive individuals have a 60-85% lifetime risk for developing colorectal cancer[7] HNPCC has also shown an accelerated adenoma-carcinoma sequence compared to sporadic colorectal cancer of 2-3years[6,8]. The mean age of developing colorectal cancer in HNPCC is 45 years; on average 20 years earlier than sporadic colorectal cancers[7.] The protocol at UCT is to do surveillance colonoscopy every two years from 16-30 years of age and yearly there after[9, 10.]

The surgical options for HNPCC remain unclear. The American Society of Colon and Rectal Surgeons recommends for HNPCC individuals with more than one advanced adenoma or cancer a total colectomy and ileorectal anastomosis(with lifelong rectal surveillance) or proctocolectomy and ilioanal pouch for rectal lesions[11].There is still a 12% risk of developing rectal carcinoma post colectomy. Segmental resections are discouraged due to the high risk of metachronous and synchronous disease (45% and 18% over 10 years respectively)[12]. Data from the Colorectal Unit in Groote Schuur Hospital (GSH) reported a 20% 5 year and 41% 15 year risk of metachronous colonic cancer in their HNPCC population[13]. Research has shown up to 29% of polyps under

5mm are missed at colonoscopy [14] and an incomplete colonoscopy rate of 3% by experienced endoscopists (up to 46% if self-trained)[15]. A 96% completion rate is achieved by the UCT colonoscopy unit in GSH as well as on community outreach colonoscopies[16]. In spite of this, prophylactic colectomies in patients without mucosal lesions should not be done due to incomplete penetrance of the disease as well as the mortality and especially morbidity associated with these procedures.

A concentration of HNPCC positive families was discovered in the 1980's in Namaqualand and surrounding areas of the Northern Cape[17]. These families have formed part of an active genetic screening and colonoscopic surveillance program led by the Colorectal Surgery unit and Department of Genetics of the University of Cape Town. This is a resource poor and remote region with limited access to specialist medical services that hampers regular follow-up. Earlier intervention in this group might be justified.

AIM:

To determine the cancer free survival of individuals identified with HNPCC via genetic testing; found to have benign adenomatous polyps on routine surveillance colonoscopy.

OBJECTIVES:

Primary Objective:

To compare the cancer free survival of biopsy proven benign adenomatous polyps in HNPCC patients receiving colonic resection with those on continued surveillance colonoscopy.

Secondary Objectives:

A. Surgical group:

1. To determine a relationship between the grade of dysplasia in the adenomatous polyps and the discovery of an unexpected cancer.

2. To determine the relationship between the number of adenomatous polyps and the chance of an unexpected cancer.

3. To determine the relationship between the anatomical location of the polyp and the chance of an unexpected cancer.

B. Surveillance group:

1. The time span to the development of colon cancer on routine colonoscopic surveillance.

METHODOLOGY:

Study design: Retrospective review of prospectively collected data of mutation positive (specifically MLH1 and MSH2) HNPCC patients on the UCT HNPCC registry. All these patients are offered surveillance colonoscopies. There is no protocol dictating management when adenomatous polyps are indentified. The decision on surgery or continued surveillance is at the discretion of the treating physician and/or the choice of the patient. The surgical specimens are evaluated for unsuspected cancer in what is preoperatively presumed to be a resection for benign disease. The surveillance group continues regular colonoscopies with biopsy to detect/exclude the transformation of the adenomatous polyps to cancer on biopsy.

Study population: All patients known with the MLH1 and MSH2 HNPCC mutation in UCT Registry up to Dec 2010.

Sampling size and method: All mutation positive HNPCC individuals found to have adenomatous polyps on surveillance colonoscopy. Sample size is limited by number of patients in registry.

Inclusion criteria: HNPCC mutation positive individuals with histologically proven benign adenomatous polyps on biopsy during surveillance colonoscopy.

Exclusion criteria:

1. Biopsy proven Colon Cancer on first surveillance colonoscopy.

2. Any form of previous colorectal surgery for malignant disease.
3. History of colorectal cancer.
4. < 18 years of age

Outcome variables:

1. Detection of unexpected cancer on resected colon specimen.
2. Development of cancer on surveillance colonoscopy.

Determinant variables:

1. Gender
2. Age at first colonoscopy that showed adenomatous polyps
3. Grade of polyps on biopsy taken at colonoscopy
4. Number of polyps on colonoscopy
5. Anatomical location of polyps on colonoscopy
6. Histology of any resected specimens
7. Time interval between colonoscopy surveillance
8. Time span from first colonoscopy to detection of cancer on biopsy.

Ethical aspects:

Patient information will be collected in such a way as to protect confidentiality throughout the study. Al subjects received formal counselling and signed written consent for genetic testing and surveillance colonoscopy. A large component of the study population is resident in remote areas of the Northern Cape making tracing of individuals for written informed consent for this study difficult. The study will adhere to guidelines of the 2008 Helsinki declaration.

Statistical analysis:

Initial descriptive statistics including measures of central tendency and variation will be calculated using Excel by the study investigator. Any further Multivariate analysis or Kaplan-Meier graph depiction of cancer free survival will be done in consultation with a qualified statistician.

Cost:

Any cost will be funded by investigator.

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