

Detection and Management of Colorectal Neoplasia in the NHS Bowel Cancer Screening Programme



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Detection and Management of Colorectal Neoplasia in the NHS Bowel Cancer Screening Programme

Abstract

Background

Screening for colorectal cancer aims to reduce mortality by detecting cancer at an earlier stage. The NHS Bowel Cancer Screening Programme (BCSP) offers faecal occult blood testing (FOBT) followed by colonoscopy for those with a positive FOBT. This thesis examines the detection and management of colorectal neoplasia in the BCSP.

Aims and Methods

1. Explore adenoma detection rate (ADR) as a measure of colonoscopic performance and examine which factors influence adenoma detection rate by analysing data gathered from the BCSP.
2. Describe the findings at 12 month surveillance colonoscopy in high risk individuals (according to adenoma surveillance guidelines in the BCSP) and explore factors which may predict findings at surveillance.
3. Describe the management of large sessile colonic polyps (LSCP) in the BCSP and explore factors which influence the choice of treatment modality (surgical or endoscopic) and subsequent outcome. A national study of LSCP management was undertaken.

Results

ADR correlated positively with other performance indicators including withdrawal time and caecal intubation rate.

The yield of advanced colonic neoplasia (ACN) at surveillance colonoscopy was 6.6%. The presence of right sided or villous lesions at baseline may predict the presence of ACN at surveillance.

121/557 LSCP (21.7%) were managed surgically, 436/557 (78.3%) were managed endoscopically. Increasing size was associated with failure of endoscopic therapy and presence of cancer in the resection specimen.

Conclusion

ADR is a satisfactory indicator of colonoscopic performance. Measures of the total number of adenomas detected are likely to be more discriminatory indicators of performance.

The optimal mean withdrawal time for adenoma detection was 10 minutes. Longer mean withdrawal times were not associated with increasing adenoma detection.

12 month surveillance for high risk individuals is justified by the yield of advanced lesions.

Larger or right sided LSCP were more likely to be managed surgically. Safe and effective management of LSCP can be delivered by a national screening programme.

To Lucy and the boys

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General Introduction

Colorectal cancer is the second most common cause of cancer related death in the United Kingdom causing around 16,000 deaths each year (Office for National Statistics, 2010). Despite advances in diagnosis and management leading to a twofold increase in five year survival over the last 30 years, the incidence of colorectal cancer has stayed much the same (Office for National Statistics, 2010).

Colorectal neoplasia is an umbrella term including both colorectal cancer and colorectal adenomas. Colorectal adenomas are the slow-growing precursor lesion to cancer. This natural history, with a long premalignant phase, offers the opportunity for pre-symptomatic detection and removal of adenomas to radically alter the natural history of the disease. The seminal National Polypectomy Study (Winawer, 1993) provided proof of concept that adenoma detection and removal could reduce the incidence of colorectal cancer.

Once an adenoma has progressed to cancer, the earlier the cancer is detected and treated, the better the outcome for the patient. There is a considerable survival advantage with earlier stage of disease at diagnosis (National Cancer Intelligence Network, 2009). Over the last 30 years there has been considerable interest in exploiting the natural history of colorectal cancer and the favourable outcome of earlier diagnosis to develop a screening strategy that could reduce the incidence and mortality of this common disease.

Whilst colonoscopy is the gold standard test for detection of colorectal neoplasia, it is time-consuming, expensive, demanding on resources and potentially harmful to the individual, limiting the appropriateness of colonoscopy as a population-wide screening test.

Three large randomised control trials (Mandel 1993, Hardcastle 1996, Kronborg 1996) conducted in the United States, the United Kingdom and Denmark demonstrated the efficacy of faecal occult blood testing (FOBt) to reduce mortality from colorectal cancer. FOBt aims to detect microscopic amounts of blood which

may be present in the faeces of individuals with advanced colorectal adenomas or cancer. As a test, it is much safer, cheaper, more acceptable and less resource intensive than colonoscopy. This is offset by much reduced sensitivity and specificity. The use of FOBt as a mass screening tool however has been widely accepted. A large scale pilot study of FOBt for the general population in the United Kingdom (UK Colorectal Cancer Screening Group, 2004) demonstrated the feasibility for such a mass screening programme to be introduced.

Two years later, the English National Health Service (NHS) Bowel Cancer Screening Programme (BCSP) was launched. This is only the third mass screening programme for cancer in England following the breast and cervical screening programmes and the first programme to include men. The screening strategy employed by the BCSP draws on the evidence available from the three large randomised control trials of FOBt and the national pilot by offering biennial guaiac-based faecal occult blood testing to all adults in England aged 60 to 69 years of age. The upper age limit was extended to 74 years in 2010. Individuals with a positive FOBt are offered colonoscopy.

The aim of the screening programme is to offer a test which identifies a subgroup of the target population at a higher risk of having colorectal neoplasia. The relatively scarce resources for colonoscopy can then be targeted towards this higher risk group. The main aim of colonoscopy within the screening programme is to detect cancer at an earlier stage, thus enabling the individual to receive earlier definitive treatment. A secondary aim of colonoscopy is to detect and remove adenomas, potentially reducing the risk of an individual subsequently getting colorectal cancer.

This thesis concerns itself with the role of colonoscopy within the English Bowel Cancer Screening Programme. Its aims, outlined below, evolved in response to the needs of the screening programme to understand more about the detection and management of colorectal neoplasia. The gaps in knowledge of how best to assess the quality of colonoscopy within a screening programme, in particular whether adenoma detection rate is a satisfactory performance indicator and what factors

influence adenoma detection rate, gave rise to the first chapter of this thesis entitled 'Detection of neoplasia in the NHS Bowel Cancer Screening Programme'.

The need to understand the outcome of surveillance colonoscopy in individuals found to have multiple or large colorectal adenomas during screening gave rise to the first part of the second chapter of this thesis, entitled 'Management of colorectal neoplasia in the Bowel Cancer Screening Programme'. The second part of this chapter examines how large colonic polyps are managed, necessitated by the absence of existing data on current clinical practice in England and the lack of clear evidence supporting either surgical or endoscopic management of such lesions.

The specific aims of each chapter are outlined below:

- **Chapter 3- Detection of colorectal neoplasia in the BCSP**
 - Examine, using univariable and multivariable analysis, the relationship between adenoma detection rate (ADR) and other performance indicators (withdrawal time, intubation rate, rectal retroversion, buscopan use, sedation use, and adverse event rate).
 - The central hypothesis is that adenoma detection rate, if it is to be widely used as a performance indicator for colonoscopy in the screening programme, should correlate with other measures of colonoscopic performance.
 - Individual factors that may affect adenoma detection rate such as age, gender, body mass index, aspirin use and socioeconomic status will be considered.
 - This work will contribute towards the development of colonoscopy quality indicators for the Bowel Cancer Screening Programme.

- **Chapter 4.1- Management of Colorectal Neoplasia in the BCSP**
 - **12 month surveillance colonoscopy for high risk individuals in the BCSP**
 - The number and type of adenomas found at colonoscopy affect how often the patient should be followed up. A patient with 5 or more adenomas or 3 or more adenomas of which one is at least 10mm in size is more likely to have a recurrence of polyps in the future and more likely to get bowel cancer. It is probably important therefore, to survey these patients more closely and perform surveillance colonoscopy at appropriate intervals. Current guidelines recommend surveillance colonoscopy at one year for patients who are at high risk of getting further adenomas.
 - In this section of the thesis the findings at colonoscopy of patients who have had both screening colonoscopy and one year surveillance colonoscopy will be compared. The work in this section will look at the factors that predict adenoma recurrence at one year. Univariable and multivariable analysis will be used to examine the factors which may predict adenoma recurrence at one year.
 - The hypothesis tested in this section is '12 month surveillance colonoscopy in patients with 'high-risk' findings at index colonoscopy is not worthwhile'.

- **Chapter 4.2- Management of large sessile or flat colonic polyps in the BCSP**
 - Large colonic adenomas (≥ 20 mm in size) comprise a subgroup of polyps for which the best approach to management is not clear.
 - A number of therapeutic options exist. These include:
 - Surgical resection- Which incurs the risks associated with abdominal surgery.
 - Endoscopic resection- Using relatively new techniques such as endoscopic mucosal resection.
 - Initial work will quantify the incidence of these polyps. The subsequent management of each polyp will be reviewed to give an insight into the use of current management strategies.
 - The main hypothesis for this section is ‘endoscopic treatment is as effective as surgical treatment for the management of large colonic polyps’.

The thesis is presented as a series of papers, which collectively address the aims outlined above. An initial methodology section will describe the Bowel Cancer Screening System (BCSS), the centralised database generated by collecting data from all individuals undergoing colonoscopy in the BCSP. Data quality and completeness in the BCSS will be reviewed and the process of defining and deriving colonoscopy quality indicators from the BCSS will be described.

Subsequently, five papers will be presented, each with a brief introduction and discussion. A general discussion at the end of the thesis will summarise the findings as well as exploring other questions raised by this work.

General Methodology

1.1.0- The NHS Bowel Cancer Screening System

The NHS Bowel Cancer Screening Programme gathers data on all patients entering the programme. Further data on patients undergoing colonoscopy are contemporaneously uploaded by Specialist Screening Practitioners and administrative staff at screening centres around England as the patient passes through the screening pathway. The data are entered via a graphical user interface (known as the Bowel Cancer Screening System-BCSS) onto an Oracle database. Data can be exported to an SQL server to allow specific queries to be written.

The benefits of the database are that the data are prospectively gathered and comprehensive. A wide range of parameters are recorded including demographics (age, sex, postcode of address at time of entry into screening programme, relevant medication history, weight and height), faecal occult blood test results, colonoscopy results, histology outcomes and subsequent management.

Access to the national database is restricted. Dr M. Rutter is chair of the National BCSP Service Evaluation Group. The body of work contained within this thesis has been sanctioned by the evaluation group. As clinical supervisor for this MD he facilitated access to the National Database. Assistance in accessing the database was provided by the NHS BCSP National Office. Requests for specific datasets were made to the National Office who provided the data in a Microsoft Excel spreadsheet.

The process of extracting the data for the purposes of this thesis from the main database was undertaken by myself in conjunction with Claire Nickerson (Data analyst, NHS Cancer Screening Programme). This involved defining the specific data that was required and writing the 'query' to the database to ensure the correct data was obtained. Additional assistance with this process was provided by data analysts from NHS Connecting for Health, based in Exeter.

The definitions and specifications of the colonoscopy quality indicators which were calculated are shown in Appendix A.

1.1.1- Data completeness and quality

During the data collection phase of this thesis over 4 million people underwent screening and over 30000 colonoscopies were performed. The completeness of the data captured by the NHS Bowel Cancer Screening Programme Database was not previously known; initial experience suggested that the relevant data fields to this thesis were well populated.

An initial exercise to assess the completeness of the dataset of adenomas detected at screening and 12 month surveillance colonoscopy showed that data fields completed at the time of the endoscopy (e.g. size and location of polyp) were well populated (97-100% complete). However, data requiring input onto the database after the procedure (such as pathology details) were not as complete (82-93.5% complete).

The main potential gap in the data is in the `histological grade` field for each polyp. The data in this field are not central to the planned analyses but will be important when looking at factors which predict adenoma recurrence.

Table 1 shows the data completeness for 2201 polyps which were found in 502 patients who underwent screening colonoscopy between August 2007 and March 2009.

	Incomplete data (number of empty fields out of 2201 fields)	Proportion of incomplete data fields
Polyp type (e.g. adenoma, metaplastic)	68	3%
Polyp size (endoscopic estimation)	92	4% 38 polyps (2.4%) have neither pathological or endoscopically assessed size field completed
Polyp size (pathologic estimation)	262	12%
Polyp Location	0	0%
Histological grade (e.g. HGD, LGD)	194	9%

Table 1 - Data completeness for polyps detected at colonoscopy during the screening episode

Table 2 shows the data completeness for 849 polyps found in 502 patients undergoing surveillance colonoscopy between August 2007 and March 2009

	Incomplete data (number of empty fields out of 502 fields)	Proportion of incomplete data fields
Polyp type (e.g. adenoma, metaplastic)	55	6.5%
Polyp size (endoscopic estimation)	22	2.6%
Polyp size (pathologic estimation)	175	20.6% 12 polyps ((1.4%) have neither size field completed
Polyp Location	0	0%
Histological grade (e.g. HGD, LGD)	150	18%

Table 2- Data completeness for polyps detected at surveillance colonoscopy

The tables above suggest high levels of data completeness. However, these data were generated by requesting details of patients who had adenomas from the national database. If adenomas detected at colonoscopy are not recorded onto the database at a local level, they will not appear in the database and thus patients with adenomas may be missed from this analysis.

A further exercise was therefore performed to assess the quality (accuracy) and completeness of the data in the BCSP database. This was undertaken in November 2009 and involved comparing the data relating to 25 patients held in BCSP database with data obtained from their original pathology and endoscopy reports. A spreadsheet containing details of all colonoscopies performed in a certain period in the Tees BCSP area and all adenomas found in the same period was generated from the Bowel Cancer Screening System central database. 25 patients were randomly identified from this spreadsheet, which contained the details of patients who had undergone colonoscopy in the Tees BCSP centre between March 2007 and March 2009.

Details of polyps recorded on the spreadsheet (which were downloaded from the BCSS database) were compared with details of polyps obtained from the patients' paper records held in the Tees BCSP screening centre office. These paper records contain the colonoscopy and pathology reports. The specific fields which were compared were:

- Number of adenomas
- Site of adenoma
- Size of adenoma
- Morphology of adenoma
- Histological type of adenoma
- Dysplasia grade of adenoma

18 adenomas were recorded in 25 patients (according to the paper records) and 20 adenomas in 24 patients according to the database. The adenoma detection rate (number of patients with one or more adenomas / total number of patients undergoing colonoscopy) was 48% according to the paper records and 56% according to the database. There is only data missing from one polyp record (size of polyp 12 from the database, see table 2).

The adenoma count for each patient was the same in the database as in the paper records in 23 of 25 patients (92%). In the 2 patients in whom there was a disparity, no polyps were documented in the paper records whilst one polyp was recorded in the database. Both of the lesions recorded in the database but not in the paper records were small tubular or tubulovillous adenomas (<1cm) with low grade dysplasia. They were the only abnormality found in each patient and would not have altered clinical management.

There were discrepancies in recording of site in 6 of 24 lesions (25%). The majority of these were minor (sigmoid colon vs. descending colon). One adenoma was recorded more than 1 segment apart in the database compared to the paper records (polyps 12 in table 2). There were discrepancies in recording of size between the database and paper records for 6 of 23 adenomas (26%). The mean difference was 3.3mm. The discrepancies would not have altered the management of any of the patients.

Morphological type of polyp (sessile vs. pedunculated), was consistently and equally reported in the database and paper records. Histological type differed in 2 of 24 polyps. One polyp was recorded as a tubulovillous adenoma in the paper records and a tubular adenoma in the database. Another was recorded as a tubular adenoma in the database but as normal colonic mucosa in the paper records. Neither of these discrepancies would have altered the management of the patient.

Dysplastic grade was recorded differently in none of the 23 adenomas

6 advanced colonic neoplasms (>1cm or high grade dysplasia) were recorded. Only 1 of these would be incorrectly classified as a non-advanced colonic neoplasm by data from the database.

In conclusion, in this sample there was good completeness of data in the BCSP database (99.5% complete).

There are minor discrepancies in recording of polyp details between the two sources. However, none of these would have led to the misclassification of a patient into normal, low, intermediate or high risk groups based on the BSG guidelines for adenoma surveillance (Atkin 2002). This suggests good quality of data in the BCSP database.

The disparity between adenoma detection rates was attributed to double counting of adenomas in the BCSS dataset due to duplicate entries for the same adenoma or counting of the same adenoma at more than one procedure. This problem was eliminated in further work by excluding duplicate lesions from calculations and by only analysing the first colonoscopic procedure in each screening round to avoid double counting of the same lesion.

A weakness of the evaluation of data completeness and accuracy described above is the limited size of the study and restriction to one screening centre. Increasing the number of records validated and number of screening centres included may have increased the reliability of the data validation process.

Limiting the exercise to one centre may have introduced bias to the assessment. The centre was known to be a well organised unit and an early-adopter of the BCSP. Data quality findings at this centre could potentially be at odds with a less well organised unit. These limitations and their implications are further discussed in section 5.9.1.

1.1.2- Ethical considerations

The work involved in this thesis is evaluation of the NHS Bowel Cancer Screening Programme. As such it is termed ‘Service Evaluation’ and prospective ethical approval is not necessary. Written confirmation of this has been obtained from the Director of the Bowel Cancer Screening Programme. As such there is no allocation to intervention groups or randomisation planned. Similar work within the field of breast cancer screening over the past 20 years has not necessitated prospective ethical approval. The use of NHS BCSP data in this thesis has been sanctioned by the director of the NHS Screening Programmes.

Confirmation of the situation regarding ethical approval of ‘service evaluation’ has been sought from the Chair of an NHS Research Ethics Committee who has approved this work as Service Evaluation. (Appendix B). The Bowel Cancer Screening Programme has PIAG (Patient Information Advisory Group) approval for use of data for service evaluation purposes.

The use of sensitive data (such as patient postcode) contained in the Bowel Cancer Screening Programme database was sanctioned by the Caldicott Guardian for the Bowel Cancer Screening Programme National Office. Compliance with the PIAG approvals held by the Bowel Cancer Screening Programme was observed.

Literature Review

2.1.0- Strategy for Literature Review

The aim of this literature review is to:

1. Provide an overview of the demographics and natural history of colorectal cancer based on evidence contained in relevant articles published in the medical literature. This overview will not be an exhaustive review of all aspects of colorectal cancer but will focus on aspects pertaining to the basis for screening for colorectal cancer and the evidence supporting population based screening programmes.
2. Critically review the available literature regarding the following specific aspects of colorectal cancer screening:
 - a. Adenoma detection rate and other performance indicators of colonoscopy.
 - b. Surveillance colonoscopy within a screening programme.
 - c. Management of large (>2cm) colonic polyps.

This section of the literature review will be a comprehensive review of the available evidence. It will provide a perspective on the current opinions on the topics outlined above and identify areas in which ongoing research for this thesis will contribute.

The literature review was performed using Pubmed for relevant publications between 1980 and 2009 (<http://www.ncbi.nlm.nih.gov/pubmed>). This time period was chosen in order to reflect modern clinical practice, articles from earlier than 1980 were included if deemed to be relevant to the subject and not outdated. The following MeSH terms were used: Colonic polyps, colonoscopy, colorectal neoplasms, early detection of cancer. These terms were selected from the United States National Library of Medicine's controlled vocabulary used for indexing articles for MEDLINE/PubMed. MeSH terminology provides a consistent way to

retrieve information that may use different terminology for the same concepts. These concepts were selected to pertain to the aims of the literature review outlined above.

Abstracts were reviewed and articles were excluded if they were in a language other than English or were not of sufficient relevance to the stated aims (see above) of the literature review. Full papers were then obtained. The reference lists of selected articles were scrutinised for additional papers (not restricted by year of publication).

Due to the wide range of topics covered by this literature review, a single quality assessment method or data extraction process could not be applied to all papers.

Where appropriate, the quality of individual studies was graded using the Centre for Evidence Based Medicine system below (Oxford Centre for Evidence Based Medicine, 2009):

Ia: systematic review or meta-analysis of randomised controlled trials

Ib: at least one randomised controlled trial

IIa: at least one well-designed controlled study without randomisation

IIb: at least one well-designed quasi-experimental study, such as a cohort study

III: well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case-control studies and case series

IV: expert committee reports, opinions and/or clinical experience of respected authorities.

2.1.1- Background

Colorectal Cancer

Colorectal cancer is the third most common cancer in the UK overall (Cancer Research UK 2009). In women it is the second most common cancer after breast cancer and is diagnosed in around 17,000 women each year. In men, it is the third most common cancer after prostate and lung cancer and is diagnosed in around 20,400 men each year (Office for National Statistics 2009, Welsh Cancer Intelligence and Surveillance Unit 2009; Information Services Division Scotland 2009; Northern Ireland Cancer Registry 2009).

It is also an important disease internationally with over 1 million people diagnosed with bowel cancer worldwide annually (Ferlay et al 2010), however it is less common in Africa and Asia than in Europe, the Americas and Australasia, either due to lower prevalence or poorer detection. This variation in incidence globally is attributed to environmental factors rather than genetic factors. In particular a western diet (rich in saturated fat, refined carbohydrates and animal protein) associated with low physical activity, is thought to predispose to colorectal cancer. The incidence of colorectal cancer in migrant communities rapidly reaches the higher level of risk of the adopted country (World Health Organisation 2003).

The colon and rectum, colloquially known as ‘the large bowel’, form the final stages of the gastrointestinal tract. The colon is around 1.5 meters long and the rectum constitutes the final 10-15cm of this. The chief roles of the colon and rectum are to:

- Transport digested food and faeces from the small bowel to the anus
- Store faeces prior to excretion
- Remove water from the faeces.

Over 90% of colorectal cancers are adenocarcinomas (cancers arising from the mucosal lining of the bowel). These cancers arise from precancerous lesions called adenomas. The pathogenesis of adenomas and their progression to cancer is described in section 2.2.

The detection of cancers at an early stage is the main aim of the NHS Bowel Cancer Screening Programme. The removal of adenomas before they become malignant is a secondary aim. This will be discussed in section 2.5.

Colorectal Cancer Demographics

Over 100 cases of colorectal cancer are diagnosed in the UK each day. The lifetime risk of colorectal cancer is 1 in 16 for men and 1 in 20 for women (Cancer Research UK 2009). The incidence of colorectal cancer increases with age. 83% of colorectal cancers are diagnosed in over-60 year olds. Colorectal cancer is more common in men with an overall male:female age standardized ratio of 1.6:1 (Cancer Research UK 2009). This male preponderance is most marked between the ages of 60 and 80 years, however there are numerically more colorectal cancer in females than males over the age of 80 years. This is a result of females living longer than males and forming the numerical majority of the elderly population (see tables 3,4).

The following definitions apply to the tables below:

Age-specific rate- The number of cancer registrations or deaths for a particular sex and age group divided by the corresponding sex- and age-specific mid-year population; usually expressed per 100,000 persons per year.

Age-standardised rate- An incidence or mortality rate which has been weighted using a standard population to control for differences in populations between geographical areas or over time, to allow unbiased comparison; usually expressed per 100,000 population years. The standard population used in figure 1 is a European standard population.

Crude rate- The crude rate is the total number of cases divided by the mid-year population, usually expressed per 100,000 population years.

	Age (years)		
	30-49.9	50-79.9	≥80
Male	770	11899	3743
Female	691	8528	4635
Total	1461	20427	8378

Table 3-Registrations of newly diagnosed colorectal cancer in the England in 2006 (Cancer Research UK 2009).

		Age specific rate					
		60-64 (years)	65-69	70-74	75-80	80-84	>85
	All ages (crude)						
Male	66.1	137.9	220.6	313.9	394.1	468.4	467.4
Female	52.5	82.6	124.1	186	248.6	307	320.7

Table 4- Age-specific rates of newly diagnosed colorectal cancer per 100,000 population in England in 2006 (Cancer Research UK 2009).

The incidence of colorectal cancer is higher in areas of greater socioeconomic deprivation. Analysis of data on the incidence of colorectal cancer in males in England between 2000 and 2004 shows an 11% greater incidence in the most deprived areas compared to the most affluent areas (National Cancer Intelligence Network 2008). Factors underlying this are not entirely clear but relate to lifestyle factors (smoking, obesity, exercise). Differing health behaviour (delayed presentation) and lack of access to healthcare services may lead to later presentation and poorer prognosis in more deprived areas (Coleman et al 2004).

Geographical variation of the incidence of colorectal cancer within the UK is relatively small however there is a higher than average incidence in Scotland and

Northern Ireland and in the north of England (See figure 1) (Quinn et al 2005). Again the reasons underlying this trend are not clear but probably relate to socioeconomic factors.

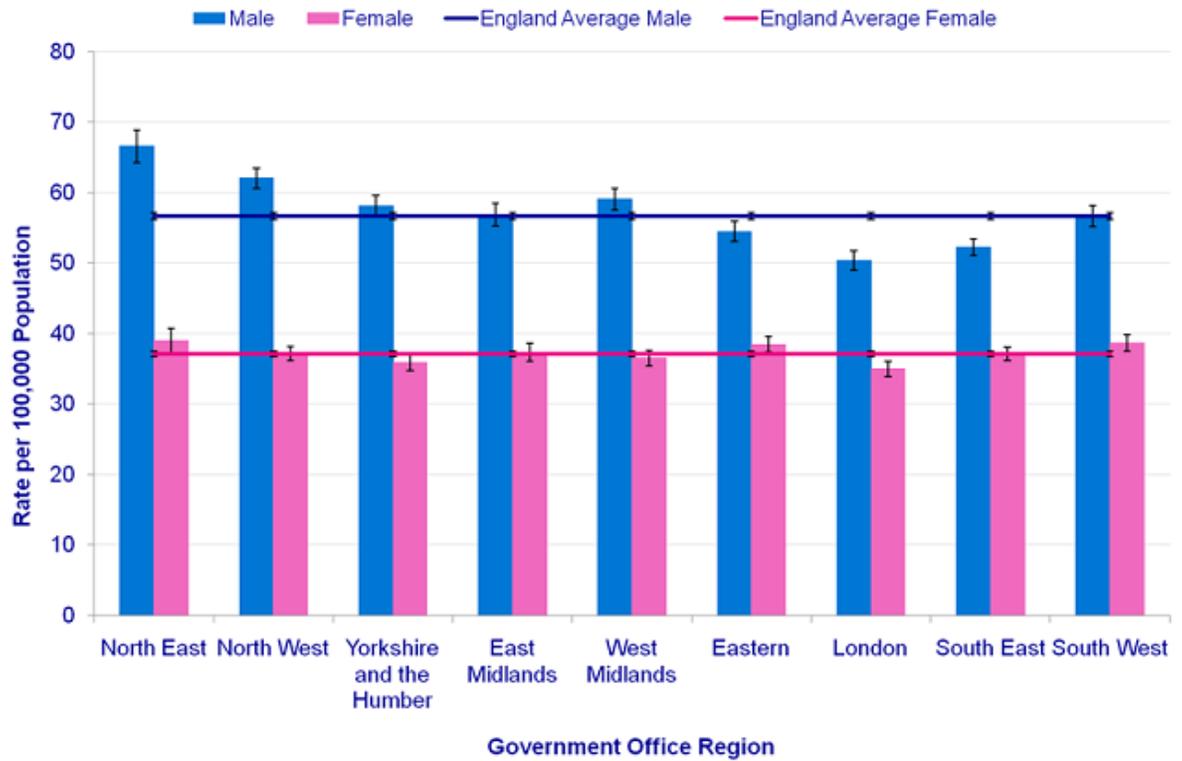


Figure 1- Age standardized incidence rates by sex, colorectal cancer and region of England, UK and Ireland, 2006-8 showing 95% confidence intervals (Cancer Research UK).

Natural history of colorectal cancer

The term colorectal cancer comprises cancers arising in two relatively distinct locations. The colon is the large bowel proximal to the rectum. The rectum is defined as the 15cm of bowel proximal to the anal verge (UKCCR 1989). The location of a cancer with regards to the colon and rectum has important implications for diagnosis and management.

The majority of colorectal cancers arise on the left side of the bowel (see figure 2). Right sided cancers are less common but emerging evidence may suggest an alternative pathological mechanism of their development (Nawa et al 2008).

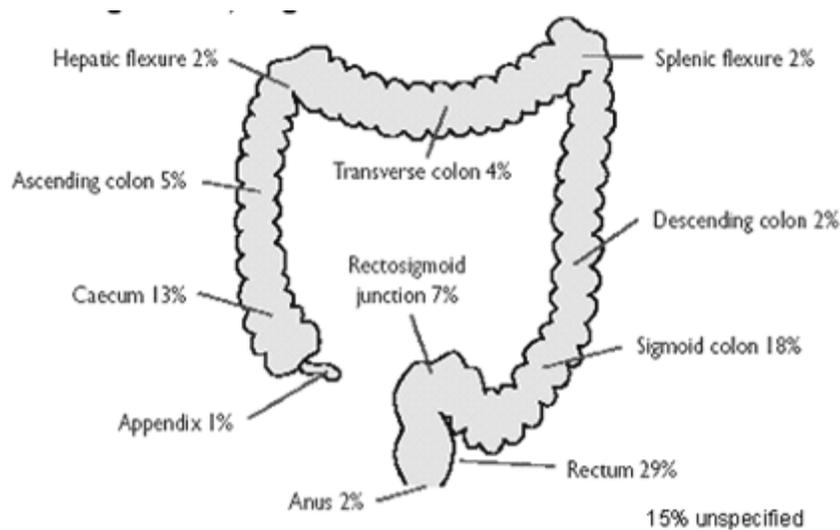


Figure 2- Percentage distribution of cases by site of colorectal cancer, England 1997-2000. (Cancer Research UK).

It has been understood for some time that the majority of colorectal cancers arise from pre-existing adenomatous polyps. A polyp is a non specific term for a lesion developing on the lining of the bowel (Vogelstein et al 1988). There are many different types of polyp. Some are benign and have no potential to become cancerous (such as hyperplastic polyps or lipomas). Some polyps are adenomas. By definition adenomas are 'neoplastic'. This term refers to the abnormal growth relative to normal tissue exhibited by adenomas. Adenomas are also 'dysplastic',

this refers to the microscopic structural and organizational changes of cells that characterise dysplasia. Dysplasia is a spectrum from mild or low grade dysplasia to cancer, so the more dysplastic an adenomatous polyp is, the more likely it is to become malignant.

The progression of normal colonic mucosa to adenoma and on to cancer was first described in the late 1980`s and is termed the ‘adenoma-carcinoma sequence’ (Vogelstein`s hypothesis) (Vogelstein et al 1988).

The association between adenoma and carcinoma was originally contentious but the following arguments have reinforced the association:

Anatomical distribution- The distribution of adenomas and cancers within the bowel is similar (Granqvist 1981).

Synchronous carcinoma- 3-7% of patients will have colorectal cancer at more than one site in the bowel at the time of diagnosis. Around one third of patients with colorectal cancer will have adenomas elsewhere in the bowel at diagnosis (Chu et al 1986; Eide 1986).

Metachronous carcinoma- Patients with polyps in addition to colorectal cancer at diagnosis are twice as likely to develop a subsequent carcinoma after resection compared to patients with no other polyps at diagnosis (Bussey et al 1966).

Age- The age related prevalence of adenomas relates well with that of carcinomas. The average age of patients with adenomas is around 5 years younger than patients with carcinomas (Muto et al 1975; Winawer et al 1975). This is consistent with the estimated duration of the adenoma-carcinoma sequence being around 10 years.

In surgical resection specimens of colorectal cancer, adenomatous tissue is often present. Muto et al found that 278 of 1961 (14.2%) colorectal cancers contained adenomatous tissue; this figure rises to 50% in early cancers (Bussey et al 1966).

Larger adenomas are more likely to display advanced neoplastic changes than smaller adenomas (Bussey et al 1966).

Familial adenomatous polyposis (FAP) is an autosomal dominant condition caused by a mutation in the tumour suppressor adenomatous polyposis coli (APC) gene on chromosome 5q. It is characterized by the presence of hundreds of colonic adenomas. The lifetime risk of colorectal cancer in these patients is virtually 100%. The adenomas in FAP are histologically identical to sporadic adenomas suggesting both have similar malignant potential (Phillips 2003).

The incidence of colorectal cancer can be reduced by programmes involving long term screening for and removal of adenomas at colonoscopy (Winawer 2003). Bond (2000) states that interruption of the adenoma carcinoma sequence by polypectomy and the resultant reduction in colorectal cancer and mortality is conclusive proof of the adenoma carcinoma sequence.

A proposed genetic basis of the adenoma carcinoma sequence is demonstrated in figure 3.

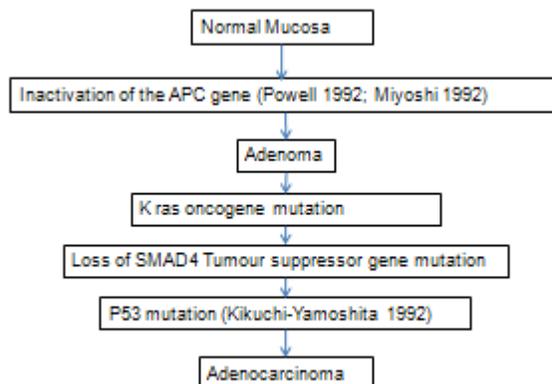


Figure 3-Accumulation of genetic mutations leading to adenomas and carcinoma

Figure 3 represents a vastly simplified sequence of genetic mutations that can transform normal mucosa to adenoma and then to cancer. These mutations occur sporadically and not all adenomas will develop such mutations.

It is estimated that the adenoma carcinoma sequence takes place over 10 years and that only a small proportion (1-10%) of adenomas complete the sequence during an

individuals lifetime (Muto et al 1975; Winawer et al 1987). More advanced adenomas (those with more dysplastic features such as being greater than 1 cm in size or displaying high grade dysplasia) progress to cancer at a higher rate (up to 5% per year (Brenner et al 2007)).

There is emerging evidence that some (the exact proportion is not currently known) colorectal cancers may develop via an alternative accelerated pathway which has become known as the serrated pathway. The premalignant lesions (sessile serrated adenomas) are characteristically morphologically flat and more likely than 'typical' adenomas to be found in the proximal colon (O'Brien et al 2000). These are more difficult to detect at colonoscopy (Nawa et al 2008; Kahi et al 2011). They are likely to develop via an alternative genetic pathway involving earlier activation of BRAF or KRAS1 resulting in activation of the MAP kinase pathway. Silencing of MLH1 by methylation causing impaired mismatch repair gene function and microsatellite instability precedes the transition to cancer (Arain et al 2010; Leggett et al 2010). The recognition of this pathway has raised the profile of proximal metaplastic lesions which were previously felt not to have malignant potential but are now recognised as precursor lesions.

Benefit of early diagnosis and treatment of colorectal cancer

The prognosis of colorectal cancer depends on the disease stage. Disease stage depends on:

1. Depth of invasion of the bowel wall
2. Presence or absence of lymph node invasion
3. Presence or absence of distant metastases.

The original staging system is the Dukes classification which is still widely used (Dukes 1932). It was originally devised by the St Mark's (London) pathologist Cuthbert Dukes (figure 4) in the 1930s for staging rectal cancer. The system however, also applies to colon cancer. The original Dukes classification was based

solely on pathological findings and did not take into account distant metastases. A modified Dukes classification to include stage D has therefore been widely adopted (table 5).



Figure 4-Cuthbert Dukes (from www.polyposisregistry.org.uk/stmarks/about.htm)

	Pathological findings	5 year survival (NCIN 2009)	Percentage of cases (NCIN 2009)
Dukes A	Tumour confined to the bowel wall with no lymph node metastases	93.2%	8.7%
Dukes B	Tumour penetrating through the bowel wall to serosa or perirectal fat with no lymph node metastases	77.0%	24.2%
Dukes C	Lymph node metastases present	47.7%	23.6%
Dukes D	Distant metastases (e.g in the liver or lungs) present.	6.6%	9.2% (Unknown 35.4%)

Table 5- Modified Dukes staging, pathological criteria, 5 year survival and distribution of cases.

The other commonly used staging classification is the TNM (Tumour, Node, Metastases- American Joint Committee on Cancer) classification. This provides greater definition in staging depth of invasion.

Stage	Criteria
T1	Tumour beyond the muscularis mucosa into the submucosa
T2	Tumour extending through the submucosa into the muscularis propria
T3	Tumour invaded beyond muscularis propria into the subserosa
T4	Tumour has breached the serosa
N0	No lymph node involvement
N1	1-3 lymph nodes close to the bowel involved
N2	4 or more nodes involved that are more than 3cm from primary or lymphovascular invasion
M0	No distant metastases
M1	Distant metastases present

Table 6- TNM classification of colorectal cancer

The TNM classification allows classification of colorectal cancer into 5 stages which can be converted to Dukes stages.

Stage	Features	Equivalent Dukes Stage
0	Tumour confined to mucosa (equivalent of carcinoma in situ)	-
1	Local invasion of tumour to muscle or serosa but no lymph node or distant spread. (T1 N0 M0 or T2 N0 M0)	A
2a	Local spread beyond bowel wall but no lymph nodes involved (T3 N0 M0)	B
2b	Locoregional invasion to adjacent organs but no lymph node or distant spread (T4 N0 M0)	B
3a	Tumour confined to bowel wall but 1-3 local nodes involved (T1 N1 M0 or T2 N1 M0)	C
3b	Locoregional invasion beyond bowel wall and 1-3 local lymph nodes involved (T3 N1 M0 or T4 N1 M0).	C
3c	Any depth of invasion with 4 or more regional nodes involved and no other distant metastases (any T N2 M0).	C
4	Distant metastases (any T, any N, M1).	D

Table 7- TNM stages of colorectal cancer with equivalent Dukes stage

5 year survival is the most commonly reported outcome measure of colorectal cancer management. This is because at least 90% of disease related events (cancer recurrence or death) will occur within 5 years of diagnosis.

Treatment of colorectal cancer depends on the site and stage of the cancer, together with patient characteristics such as age and comorbidities.

Non-malignant adenomas can usually be removed endoscopically without the need for surgery. Very large adenomas or those harbouring advanced neoplasia may require surgical resection (see section 4.2).

Cancer confined to a polyp (called ‘polyp cancer’) may also be managed endoscopically as the risk of local involvement of lymph nodes is relatively low.

Dukes A and B colorectal cancer invariably necessitates surgery to provide a cure. The addition of post operative chemotherapy to surgery improves survival in Dukes C cancer (Dube et al 1997).

Management options for metastatic (Dukes D) colorectal cancer include chemotherapy and palliative surgery but survival is poor in this group with a median survival of around 6-12 months (Cochrane colorectal cancer group 2000).

It is clear that diagnosis and treatment of colorectal cancer at an early stage provides considerable survival advantages to the patient. If a patient is diagnosed with Dukes A cancer, they have around a 90% chance of surviving 5 years. If however, they are diagnosed at Dukes stage C, their five year survival drops to around 50% (Cancer Research UK 2009). The main aim of a screening programme for colorectal cancer is therefore to diagnose cancers earlier in order to confer these survival benefits.

The evidence for the protective benefit of adenoma removal is largely based on historical studies and observational data. Prospective randomised control trials of polypectomy for adenomas with observation as control are not feasible for ethical reasons. Important data are available from randomized trials of different surveillance strategies following polypectomy.

A study of serial barium enemas performed in the era before colonoscopy was available monitored polyps larger than 1cm left in situ over many years. It demonstrated a cumulative risk of malignancy at 5,10 and 20 years of 2.5%, 8% and 24% (Stryker 1987).

An important report from the US National Polyp Study provides direct evidence of the protective benefit of colonoscopy and polypectomy (Winawer 1993). This was a pooled study of all 1418 subjects who had undergone colonoscopy and had at least one adenoma removed. Patients were randomized to undergo surveillance colonoscopy at either 1 year, 3years and every 3 years subsequently or to miss the 1 year examination and have 3 yearly surveillance. A lower incidence of colorectal

cancer in the surveillance period (average length was 5.9 years) compared to incidence in 3 different reference populations was observed. The incidence of subsequent colorectal cancer was reduced by 76-90% ($p < 0.001$).

Several studies have demonstrated the protective benefit of sigmoidoscopy and polypectomy resulting in reduction in distal colorectal cancer incidence and mortality from colorectal cancer. In Minnesota, 21,000 individuals underwent annual screening rigid sigmoidoscopy and polypectomy over a 20 year period. Incidence of rectal cancer in the study group was reduced by 85% compared with the known incidence in Minnesota (Gilbertsen et al 1992). Two U.S. case-control studies comparing rates of colorectal cancer in patients who had undergone screening sigmoidoscopy with matched controls suggest a reduction in mortality from distal colorectal cancer of 60 and 80% respectively (Selby et al 1992; Newcomb et al 1992). In the first of these trials (Selby et al 1992) the protective benefit lasted for up to 10 years and proximal cancer rates were similar in both screening and control patients. A similarly designed case-control study, this time of flexible sigmoidoscopy, colonoscopy and polypectomy in 32,702 U.S. patients demonstrated a 50% reduction in risk of developing colorectal cancer with protection lasting 6 years (Muller et al 1995).

Screening for colorectal cancer

Screening is defined by the UK National Screening Committee (2011) as:

‘a process of identifying apparently healthy people who may be at increased risk of a disease or condition. They can then be offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition.’

For a disease to be amenable to screening it should fulfil the criteria laid out by Wilson and Jungner for the World Health Organisation in 1968. These criteria are shown in table 8 with details relevant to colorectal cancer shown in the right hand column.

Wilson and Jungner Criteria (paraphrased)	Evidence supporting screening for colorectal cancer
The condition is an important health problem	3 rd most common cancer in the UK (Cancer Research UK 2009)
Its natural history is well understood	Adenoma-carcinoma sequence (Vogelstein 1988)
It is recognisable at an early stage	Premalignant lesion is the adenoma
An acceptable treatment exists	Polypectomy or surgery are acceptable treatments.
A suitable test exists	Faecal occult blood (FOB) testing has sensitivity for colorectal cancer of 50-70% (Steele 2005).
An acceptable test exists	FOB testing is accepted by approximately 50% of those invited.
Adequate facilities exist to cope with abnormalities detected	Colonoscopy and surgical services are adequately equipped to cope with demand (Dent et al 2009)
Screening is carried out at repeated intervals when the onset is insidious	Trials of FOB testing have used a biennial FOB test strategy.
The chance of harm is less than the chance of benefit	FOB testing is safe.
The cost is balanced against benefit	Similar cost effectiveness to breast cancer screening in the short term. Possibly superior in the long term (Whynes et al 1998)

Table 8- Criteria for a disease to be suitable for screening (after Wilson and Jungner 1968)

Colorectal cancer therefore, is a disease which should be suitable for screening. Wilson and Jungner`s criteria do not explicitly mention that early treatment of the disease in question should be favourable, however, this requirement is also a desirable characteristic of a condition amenable to screening. With respect to colorectal cancer, 5 year survival of Dukes A cancer (early stage) is 93%; 5 year survival of Dukes D cancer (more advanced) is 7% (NCIN 2009).

In light of this theoretical evidence that colorectal cancer should be amenable to screening, numerous studies have examined various approaches to colorectal cancer screening. Colonoscopy is the current ‘gold-standard’ test for adenomas and

colorectal cancer. Mass population screening in the UK using colonoscopy is not economically or logistically viable as manpower and financial resources could not currently permit every adult of a certain age to undergo colonoscopy, in addition the potential harms and risks of colonoscopy would need to be taken into account. The use of colonoscopy for mass population screening however, is employed in the USA where guidelines recommend average risk adults should undergo colonoscopy at 50 years of age and subsequently every 10 years (Winawer et al 2003).

In the UK an alternative approach is required which allows mass population screening, is economically viable and is safe and acceptable for patients. The most widely studied test that fulfils these criteria is faecal occult blood testing (FOBT). Faecal occult blood testing is based on the peroxidase-like activity of haematin in faeces on guaiac (a phenolic compound derived from wood resin extracted from trees in the genus *Guaiacum*). When hydrogen peroxide is added to guaiac, oxidation occurs resulting in a colour change to blue. This reaction is very slow but the pseudoperoxidase activity of haematin (if present in blood in stool) catalyses the reaction so that it takes place in seconds.

Faecal occult blood testing relies on the fact that adenomas, particularly advanced adenomas and colorectal cancers tend to bleed. This bleeding is intermittent and at a slow rate and is due to a combination of their vascular structure and trauma from passing faeces. The peroxidase-like activity of haematin diminishes as it passes through the gastrointestinal tract reducing the chance that upper gastrointestinal bleeding will cause false positive results. Ingestion of animal haemoglobin or peroxidase containing vegetables however, may cause false positives, therefore dietary restriction can be recommended, particularly if the FOBT result is equivocal (Robinson et al 1993).

The particular type of FOBT that has been most extensively studied is Haemoccult. There are two distinct methods of processing a guaiac-based FOB test: the stool sample can be rehydrated prior to analysis, this results in more positive test results

and higher false positive rate than the alternative, which is to not rehydrate the sample (Mandel et al 1999).

FOB testing to screen for colorectal cancer is not a new concept. It's use was first described by Greigor in 1971. In this study 900 asymptomatic adults underwent FOB testing over a 3 ½ year period. 5% were FOB test positive and underwent barium enema examination. 1% (12 cases) were found to have colon cancer. The author concludes, with some prescience, that 'every adult should have this screening test annually'.

Three large prospective randomised control trials of FOB testing have been conducted in Minnesota (USA) (Mandel et al 1993), Funen (Denmark) (Kronberg et al 1996) and Nottingham (UK) (Hardcastle et al 1996). The details of each trial are given in table 9.

The Funen and Nottingham trials have similar outcomes when the groups of patients undergoing biennial screening with non rehydrated FOB testing are compared. This method of screening reduces mortality from colorectal cancer by 15-18% (Kronberg et al 1996; Hardcastle et al 1996). In both trials the rate of positivity of the FOB test was between 0.9 – 3.8%. This resulted in the cumulative proportion of screening participants undergoing colonoscopy being around 5%. In the Minnesota trial a rehydrated FOB test (Haemoccult) was used. This is a less sensitive test. It resulted in 28% of participants requiring colonoscopy in the biennial screening group and 40% requiring colonoscopy in the annual screening group but led to reductions in mortality from colorectal cancer of 21% and 33% respectively (Mandel et al 1993). It is possible that the benefits in this study were due to the high proportion of patients having colonoscopy rather than the FOB test itself.

The Funen and Nottingham trials were the only truly randomised control trials in which a population based approach was taken. The Minnesota trial required participants to volunteer to participate, after which they were randomised. This may have contributed to higher compliance (uptake of FOB testing) in the US study (75-

78% in Minnesota) compared to uptake in the European studies (53.4% in Nottingham, 56% in Funen).

This relatively lower uptake of FOB testing in the English and Danish studies may have diluted the effect on mortality and contributed to the finding that neither of the European trials demonstrated a reduction in colorectal cancer incidence over the course of the trial (Scholefield et al 2002, Jorgensen et al 2002). The Minnesota trial however, did demonstrate a statistically significant reduction in mortality of 33% in the annual group (RR 0.67 (0.51-0.83) and 21% (Risk ratio 0.79 (0.62-0.97) in the annual group (Mandel et al 2000). The Minnesota trial also demonstrated a statistically significant reduction in colorectal cancer incidence of 17% in the biennial group and 20 % in the annual group. This however, was at the expense of the high cumulative colonoscopy rates (28% and 40% respectively) described above.

In all three trials a much higher proportion of early cancers were detected in the screening group than the control group. In the Funen study 36% of cancers were Dukes A in the screening group compared to 11% in the control group (Kronberg et al 1996).

The outcomes described above suggest the screening programme trials were successful. The results should be interpreted with caution as these large trials of biennial FOB testing to screen for colorectal cancer have some limitations and are subject to the following inherent biases (Steele 2005):

Selection Bias- This arises from the tendency of particularly healthy and health-conscious people to take up the offer of screening, who may not be typical of the underlying population. This effect is said to account for the minimal reduction of 6% in colorectal cancer mortality seen in the first phase (1976-1982) in the biennial screening group of the Minnesota study (Mandel et al 1993). The effect diminished with extended follow up so that in phase 2 (1986-92) the reduction in mortality became 21%.

Length bias- This describes the tendency of screening programmes to detect more slow growing cancers during the asymptomatic phase of the cancer. Such cancers have a good prognosis anyway, leading to a favourable impact on survival of screen detected compared to non-screen detected cancers. Non-screen detected cancers are more likely to be faster growing lesions, associated with poorer prognosis.

Lead-time bias- This is based on the difference between the time at which a cancer is detected in a screening programme and when the cancer would have been diagnosed had the patient not been screened. Survival is measured from the date of diagnosis thus it can be lengthened by screening without necessarily impacting on the time to death. Equally, screening can pick up many of the prevalent cancers in a population which may have gone unnoticed had it not been for screening

Overdiagnosis bias- Screening is capable of detecting very early lesions (such as small adenomas). These are unlikely to cause any health problems during a patient's lifetime. Because these lesions are more likely to be found in a screening group than a non-screened group, comparisons may favour the screening group. Overdiagnosis bias and length bias may have similar effects on survival data however length bias refers specifically to the timing of the screening test with respect to the natural history of the disease whilst overdiagnosis bias refers to the clinical relevance of preclinical disease.

The Nottingham and Funen trials were both randomised, controlled trials which demonstrated strong age and sex comparisons between the intervention and control groups (Hardcastle et al 1996; Kronberg et al 1996). In addition, colorectal cancer mortality was used as the primary outcome measure in both trials. These factors contribute to minimising the impact of the biases described above. The Minnesota trial randomised patients only after they had volunteered to take part. This may have introduced selection bias and limit the external validity of the trial.

	Date Follow up period	Inclusion Criteria	Screening test	Screening Programme	Participation	Uptake of the FOB test	Size	Colonoscopy Rate
Minnesota Colon Cancer Control Study Mandel et al 1993,1999, 2000	Phase 1 1976-1982 Phase 2 1986-1992 Mean follow up 13 years	Age 50-80 years Volunteers from American Cancer Society and fraternal, veterans and employer groups.	First 3 years- non rehydrated FOBT. From year 3 all Rehydrated Haemoccult (with dietary restrictions)	2 groups: Annual screening Biennial screening In 2 phases over 11 years	Annual group- 90.2% completed round 1, 46.2% completed all rounds. Biennial group- 89.9% completed round 1, 59.7% completed all rounds	Annual group- 75% compliance Biennial group- 78% compliance	46551 participants Annual group- 15570 Biennial group- 15587 Control group- 15394	Annual group- 40% underwent colonoscopy Biennial group- 28%
Nottingham Hardcastle et al 1996, 1999, 2002	Pilot 1981- 83 Main study 1985-1991 Follow up ceased 1995 Mean follow up 7.8 years (range 4.5- 14.5)	Age 45-74 years From General Practice registers. Randomisation by household	Non rehydrated Haemoccult (no dietary restrictions, except for retests after a positive FOBT)	Biennial screening. Participants offered tests between 3-6 times over 14 years.	53% completed round 1. 38.2% completed all rounds	53.4% uptake overall	152850 participants Screening group- 75253 Control group- 74998	Cumulative proportion of those undergoing at least one colonoscopy= 4%
Funen Kronborg et al 1996, 2002, 2004	1985-1995 5 rounds Mean follow up 10 years	Age 45-75 years From the island of Funen population registers.	Non Rehydrated Haemoccult II (with dietary restrictions)	Biennial screening in 5 rounds over 10 years	67 % completed round 1. 45.9% completed all 5 rounds	56% uptake overall	61933 participants Biennial group – 30967 Control group- 30966	Cumulative proportion of those undergoing colonoscopy- 5.3%

	Positivity rate of FOB test	Sensitivity and Specificity of FOB test for colorectal cancer	Reduction in colorectal cancer mortality	Effect on colorectal cancer incidence	Dukes stage of screening detected cancers	Dukes stage of control group cancers	Interval cancers	Complication of colonoscopy
Minnesota	9.8%	Rehydrated FOBT: Sensitivity- 92.2% Specificity- 90.4% Non rehydrated: Sensitivity- 80.4% Specificity- 97.7%	At 18 years follow up: Annual group- 33% (RR 0.67 (0.51-0.83)) Biennial group 21% (Risk ratio 0.79 (0.62-0.97))	At 18 years: Annual group- 20% reduction in incidence Biennial group- 17% reduction in incidence	Annual group- Dukes A- 30.2% Biennial group- Dukes A- 26.6% Annual group- 47% reduction in Dukes D, Biennial group – 32% reduction in Dukes D compared to control group.	Control group- Dukes A- 22.3%	Not reported	Out of 12246 colonoscopies 4 perf, 11 serious bleeds (0.12% risk of serious complication)
Nottingham	2.1% +ve in first round. 1.2% +ve in subsequent rounds	Sensitivity- 53.6% Specificity estimated at 96-98%	13% (95% CI 3-22%) at median follow up of 11 years (p=0.01) Risk ratio 0.87; CI 0.78-0.97 p=0.01	Not reported	Dukes A- 20%	Dukes A- 11%	28% of cancers were interval cancers (26% screening, 46% in non uptakers)	Cardiovascular complications- 6.4/1000py 7/1474 (0.5%) colonoscopy complication, (5 perfs, 1 bleed, 1 other, no deaths)
Funen	1st round- 1% +ve. 0.9-3.8% in subsequent 4 rounds. Cumulative risk of a +ve FOBT- 5.7%	Sensitivity- 82% Specificity estimated at 98%	At 17 yrs: 16% reduction in colorectal cancer mortality* (RR 0.84 (0.73-0.96)) 11% reduction if complications of treatment included (not significant)	Not reported	Dukes A- 36% (72/199)	Dukes A- 11% (162/889)	Screening cancer- 199 (26%) Interval cancers- 239 (32%) Cancers in those refusing invitation- 306 (41%)	‘No deaths from colonoscopy itself’

	Lost to follow up	Compliance with colonoscopy Completeness of colonoscopy	Positive predictive value for adenoma >=10mm	Positive predictive value of FOB test for colorectal cancer	Number of colorectal cancer cases	Number of colorectal cancer deaths	Number of deaths from colorectal cancer and complications of treatment	All cause Mortality
Minnesota	Follow up statistics complete at 17 years for: 91.3% of annual group, 91.7% of biennial group, 91.2% of control group	95% Annual group- 83%, Biennial group- 84% received complete colonoscopy or flexSig+BaEnema	Annual group- 5.99% (1 +ve slide), 7.87% (6 +ve slides) Biennial Group- 6.86% (1 +ve slide), 10.08% (6 +ve slides)	Annual group- 0.87% (1 +ve slide), 4.53% (6 +ve slides) Biennial group- 1.12% (1 +ve slide), 6.13% (6 +ve slides)	Annual group- 323 (1.75/1000 py) Biennial group 323 (1.76/1000 py) Control group- 356 (1.96/1000 py)	Annual group- 121 (9.46/1000) Biennial group- 148 (11.2/1000) Control group- 121 (14.9/1000)	Not reported	Annual group- 5236 (342/1000) Biennial group- 5213 (340/1000) Control group- 5186 (343/1000)
Nottingham	2599 (1.7%) participants lost to follow up (Excluded from analysis.	Not reported	Adenoma 10-19mm screened 25%, control 35% Adenomas >19mm screened 27%, control 27%	First screen 9.9% Rescreen within 27 months 11.9%	Screening group- 1268 (1.51/1000py) Control group- 1283 (1.53/1000py) py= patient years	Screening group- 593 (0.7/1000py) Control group- 684 (0.81/1000py)	Not reported	Screening group- 20421 (24.18/1000py) Control group- 20336 (24.11/1000py)
Funen	6 persons	93.2% 89.9%	1st screening 31.6% 9th screening 22.1%	1st screening- 17.2% 9th screening- 16.5%	Screening group 889 (2.06/1000py) Control group 874 (2.02/1000py)	Screening group 362 (0.84/1000) Control group 431 (1/1000)	Screening group 427 (0.99/1000) Control group 479 (1.1/1000)	Screening group 12,205 (28.3/1000) Control group 12,248 (28.4/1000)

Table 9- Comparison of the three large controlled trials of FOB screening for colorectal cancer

A Cochrane Collaboration review and meta-analysis of screening for colorectal cancer using FOB testing has been performed (Hewitson 2007). This review excluded 10 trials of colorectal cancer screening as they were either non randomised or non controlled or only screened patients once. 4 trials were reviewed in greater detail, the 3 trials described above (Mandel et al 1993; Hardcastle et al 1996; Kronberg 1996) and a trial from Göteborg, Sweden (Kewenter et al 1994). This trial only included patients aged 60-64 years and used sigmoidoscopy and double contrast barium enema to investigate a positive FOB test. The three trials considered in more detail have more relevance to the design of the English Bowel Cancer Screening Programme as they employed biennial screening with FOB testing followed by colonoscopy to investigate a positive result.

The meta-analysis of the trials demonstrated a 15% reduction in the relative risk of colorectal cancer mortality (risk ratio 0.85, 95% confidence interval 0.78-0.92). Due to the high number of patients not complying with FOB testing in these trials (33-46% in the first screening round and 22-40% in at least one screening round) the reduction in colorectal cancer mortality adjusted for attendance was calculated as 25% (risk ratio 0.75, 95% confidence interval 0.66-0.84) for those screened.

The review concluded that colorectal cancer screening led to a 'modest reduction in colorectal cancer mortality and a possible reduction in incidence through the detection and removal of adenomas, and potentially, less invasive surgery that earlier treatment of colorectal cancers may involve'. This suggests that FOB screening may avoid approximately 1 in 6 colorectal cancer deaths. The review also warned of the harmful effects of screening which include:

- Psychosocial consequences of a false positive result (unnecessary colonoscopy)
- Complications of colonoscopy
- False negative results (interval cancers)
- Possibility of overdiagnosis (leading to unnecessary investigations or treatment)
- Complications associated with treatment

A summary of the key findings from these three main trials are as follows:

- 15% reduction in colorectal cancer mortality by biennial non rehydrated FOB testing (Hewitson et al 2007).
- 25% reduction in colorectal cancer mortality amongst those attending for screening (Hewitson et al 2007).
- No significant difference in all cause mortality between the control and screening groups in any of the trials. (RR 1.00, 95% confidence interval 0.99-1.03) (Hewitson et al 2007).
- Modest attendance for FOB testing in the Nottingham trial (53% in the first round, 38.2% completed all three rounds) (Scholefield et al 2002).
- The sensitivity of non-rehydrated FOB testing for colorectal cancer is 55-57%. (Defined as the proportion of all cancers detected by screening where 'all cancers' is the sum of screen-detected cancers (true positives) and interval cancers within 2 years of screening (false negatives)) (Hewitson et al 2007).
- The positive predictive value of non-rehydrated FOB testing is 5-18.7%, based on FOB positivity rates of 0.8-3.8% (Hewitson et al 2007).
- The positive predictive value of rehydrated FOB testing is 0.9-6.1% based on FOB positivity rates of 1.5-15.4%.
- Use of rehydrated FOB tests increases sensitivity to 82-92% but at the expense of much higher colonoscopy rates and lower positive predictive value of FOB testing.

Despite the apparent benefits of a population screening approach to colorectal cancer, arguments against such a programme exist. These are as follows:

- FOB testing fails to identify 20-50% of colorectal cancers and up to 80% of adenomas.
- The specificity of FOB testing is low and can depend on whether patients have eaten certain peroxidase containing food types beforehand.
- Sensitivity may be increased by rehydrating the FOB test but this is at the expense of specificity which would result in many more people requiring colonoscopy.
- Prior to introduction of the NHS BCSP there was concern that colonoscopy services within the UK were already stretched and would not be able to absorb the increased workload a screening programme would impose. Similar concerns existed for the pressures on radiology and pathology services (Bowles et al 2004). Investment in endoscopy infrastructure has meant that these concerns have not been borne out.
- In the Nottingham trial, 28% of cancers were 'interval cancers' - cancers diagnosed after a negative FOB test or negative colonoscopy and between screening rounds.
- The proportion of advanced cancers (Dukes D) in the control and screening groups of the Nottingham and Funen trials were unchanged. The reduction in stage at diagnosis was due to a shift from Dukes C to Dukes A disease.
- Population screening with flexible sigmoidoscopy is more sensitive and specific for distal cancers and polyps than FOB testing (Atkin et al 1996). However, it is a more invasive test than FOB entailing bowel preparation, potential discomfort and the risk of perforation or bleeding. 30-40% of cancers arise proximally to the reach of the sigmoidoscope and thus would be missed. However, distal adenomas may serve as a marker for such lesions (Atkin et al 1992) and would prompt colonoscopy in such patients. This may detect up to one third of proximal cancers (Atkin et al 1993). A randomised controlled trial of one-off sigmoidoscopy

between the ages of 55 and 60 demonstrated a 23% reduction in colorectal cancer incidence and a 31% reduction in colorectal cancer mortality but no effect on proximal cancer incidence or mortality was demonstrated (Atkin et al 2010).

- Compliance with FOB testing is modest (around 55% in the Nottingham trial). More deprived socioeconomic groups have even lower uptake (Whynes et al 2003). Increasing uptake is a significant challenge. Uptake of the screening test in other screening programmes (breast and cervical), is much higher (75% in the NHS Breast Cancer Screening Programme) (NHS Breast Cancer Screening Programme 2006).
- To prevent one colorectal cancer death in the Nottingham trial, 1250 people (95% confidence interval 690-9090) had to be offered screening over an 8 year period. This could be seen as a significant burden on society for limited benefit. There is also a risk that false positive FOB tests impose a significant physical and psychological burden on individuals (Marshall 2000).

Cost-effectiveness analysis of colorectal cancer screening using biennial FoB testing has been conducted (Whynes et al 1998). This work showed that the cost per QALY gained using data from the Nottingham study was £5685 for men and £4951 for women. Cost-effectiveness is greater in women than in men due to their increased life expectancy. This analysis is limited as it does not take into account the indirect costs of colorectal cancer screening such as psychological costs associated with anxiety and it does not include the costs of implementing a mass screening programme. A separate analysis of the cost effectiveness of faecal occult blood testing estimated the cost per life year saved as £5900 per life year saved (Steele et al 2004). This is less than the threshold at which healthcare interventions are considered to economically acceptable, the median intervention costs of 500 'life-saving interventions' was estimated at £26,000 per life-year saved by Tengs et al in 1995.

Colorectal cancer screening and surveillance in non 'average risk' populations.

The approaches to screening described above are only suitable for mass population screening of 'average risk' individuals. Certain groups of individuals are at higher risk of colorectal cancer due to underlying medical conditions or genetic and or familial predisposition. Such individuals should have screening strategies in place appropriate to their individual risk and are not suitable for inclusion in population screening programmes. Examples of high risk groups are:

- Familial Adenomatous Polyposis
 - Dominantly inherited condition, constitutes 0.5% of all colorectal cancers. Due to mutation in the APC gene on chromosome 5q, almost 100% risk of colorectal cancer by middle age. It is associated with duodenal polyposis and other extraintestinal manifestations. Known family history in 80%, 25% are due to sporadic mutation (Bisgaard 1994). Genetic screening of at risk individuals is recommended. Prophylactic colectomy or proctocolectomy for affected individuals is usually necessary.
- Peutz-Jeghers Syndrome (PJS)
 - Autosomal dominant syndrome defined by presence of hamartomatous polyps in the small and large intestine in association with mucocutaneous pigmentation. The risk of colorectal cancer is 10-20% (Giardiello 1987). Surveillance is required every 2-3 years.
- Hereditary Non-Polyposis Colorectal Cancer (HNPCC)
 - Constitutes 2% of all colorectal cancers. It results from a mutation in one of five DNA mismatch repair genes. Average age at diagnosis of colorectal cancer is 45 (compared to 65 in background population. Cancers in this group tend to be proximal and synchronous in the bowel and have characteristic pathological features. HNPCC is associated with extracolonic cancers such as endometrial (in 40% of women) and stomach

cancer (in 15%) (Aarnio 1995). Colonoscopy is recommended every 2 years from age 25 or 5 years younger than the youngest affected relative (Dunlop 2002; Cairns et al 2010). Screening for extracolonic cancers may be necessary.

- Family history
 - This may constitute up to 30% of colorectal cancers. Risk of colorectal cancer may be 2 to 6 times that of the general population in low and moderate risk groups. Requirement for colonoscopic surveillance depends on the family history (Cairns et al 2010).
- Inflammatory Bowel Disease.
 - Patients with ulcerative colitis or Crohns colitis, are at increased risk of colorectal cancer (Devroede 1971, Cairns et al 2010).
 - Current guidelines recommend surveillance should commence 8-10 years following onset of symptoms and 1-3 yearly thereafter (Cairns et al 2010).
 - Using dye spraying techniques to target biopsies may be a more effective surveillance methodology that taking multiple non targeted biopsies (Rutter et al 2004, NICE 2011).

Origins and structure of the NHS Bowel Cancer Screening Programme

As a result of the findings of the three large trials of biennial FOB testing described above, the Department of Health commissioned a pilot screening programme to assess the feasibility of using biennial FOB testing to screen the UK population. Two areas in the UK (Coventry, Warwickshire in England and Tayside, Grampian and Fife in Scotland) introduced screening programmes from 2000 onwards, inviting men and women aged 50-69 years for screening. The initial report of the UK Colorectal Cancer Screening Pilot (UK CRC Screening Pilot Evaluation Team 2003) concluded that similar outcomes in terms of test positivity, positive predictive value and shift in stage of screening detected cancers were observed in the pilot studies as in the Nottingham trial. Uptake of FOB

testing in the pilot project was around 60%. Lower uptake in certain sub-groups was noted. These sub-groups included men, younger people, those from more deprived areas and individuals from ethnic minorities, particularly Asian groups (Whynes et al 2003, UK CRC Screening Pilot Evaluation (Ethnicity) Team 2003).

478,250 individuals were invited to take part in the screening pilot. As mentioned previously, the uptake of FOB testing was 56.8% (271,646 individuals). The rate of positivity of the FOB test was 1.9% and the rate for detecting cancer was 1.62 per 1000 people screened. The positive predictive value of a positive FOBt result was 10.9% for cancer and 35.0% for adenomas (UK CRC Screening Group 2004). 552 cancers were detected by screening. 17% were polyp cancers. 48% were Dukes stage A.

The report concluded by recommending a screening programme of biennial FOB testing for the UK to the Department of Health.

A review of the second round of the pilot (Weller et al 2007) noted a lower uptake of FOB testing (52.1%). Second round positivity of FOB tests was 1.77% which was higher than expected based on findings in round one and in previous studies, the reasons for this are not clear. A lower cancer detection rate was observed in the second round of the pilot compared to the first round and the similar group of patients in the Nottingham trial. The findings of this report contributed to the 'roll out' of the national programme.

One other conclusion of note in this report was that there is need for more evidence to achieve national consensus on the optimal colonoscopy intervals for adenoma/polyp surveillance. The section of this thesis examining surveillance of patients with 'high risk' adenomas will contribute to knowledge in this area.

Subsequently the Department of Health 'rolled out' the NHS Bowel Cancer Screening Programme for England from July 2006 onwards. Coverage by the BCSP in England is shown in figure 5. Scotland, Northern Ireland and Wales have similar but separately organised programmes.

The screening programme in England consists of five programme hubs across the country operating a national call and recall system to send out FOB testing kits to eligible individuals (figure 6). Adults aged between 60 and 69 years are currently being screened. Patients over 70 years may opt in. Extension of the screening programme to include 70-74 year old adults is being rolled-out across England (figure 5). FOB testing is performed according to a protocol designed to optimise sensitivity and specificity of the test

No dietary restriction is recommended prior to completion of the test. Individuals receive the kit by mail and, after completion, return it by mail to the screening Hub in the World Health Organization (WHO) approved postage paid envelope provided within 14 days of the first sample. When repeat testing is required, this is performed within 13 weeks of previous test. All FOB kits are assessed on the day they are received by the hub by trained individuals. Quality assurance consists of continuous internal and external assessment for both FOB kits and kit readers to ensure that standards remain high. Table 10 shows how FOBt are interpreted and when repeat testing is necessary.

	Criteria	Action
Normal	No positive windows	Discharge to next screening round in 2 years
Unclear	1-4 positive windows	<p>Patient given up to 2 further FOBt kits.</p> <p>If either subsequent FOBt is unclear or abnormal, patient is referred for colonoscopy. These are classified as a 'weak positive' result.</p> <p>If both subsequent FOBt kits are normal, discharge to next screening round</p>
Abnormal	5 or 6 positive windows	Patient referred for colonoscopy.
Technical failure or spoiled kit	Lab processing problem or unreadable kit due to incorrect use	Further FOBt kit sent

Table 10- Classification of FOBt results (from Lee et al 2011).

Screening centres (up to 20 per hub (figure 7)) then provide endoscopy services and specialist screening nurse clinics to individuals as necessary. For instance if a patient had a positive FOB analysed at the hub they would be invited to a screening centre for colonoscopy closer to their home. Patients found to have cancer are managed and followed up through the colorectal multi-disciplinary meeting at the patient's local hospital. Adenoma management and surveillance are coordinated by the screening programme along current BSG guidelines (Atkin et al 2002, Cairns et al 2010).

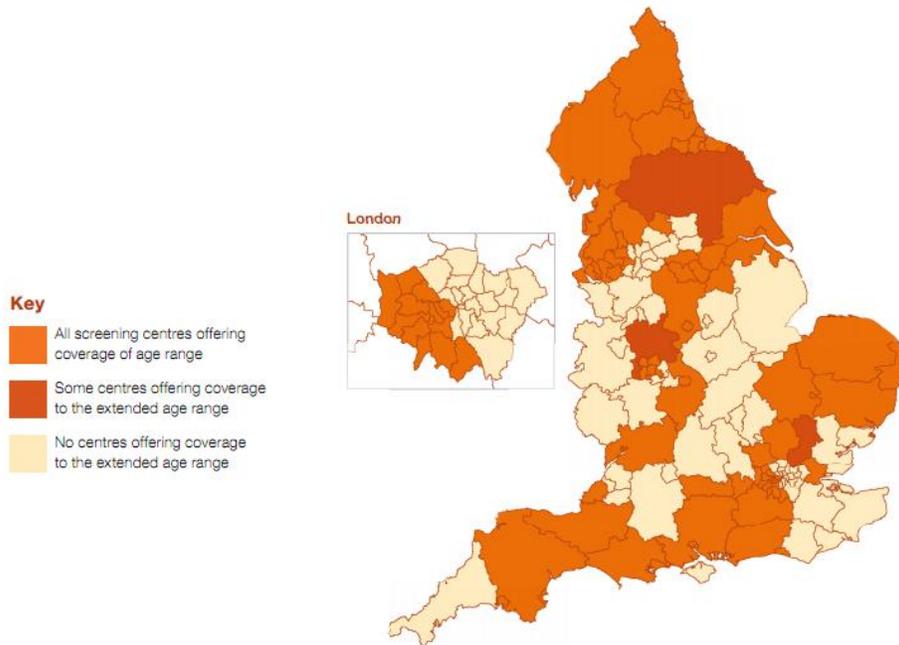


Figure 5- National coverage of the BCSP in June 2011 including roll-out of the age extension (from <http://www.cancerscreening.nhs.uk/bowel/publications/in-the-loop-summer-2011.pdf>)

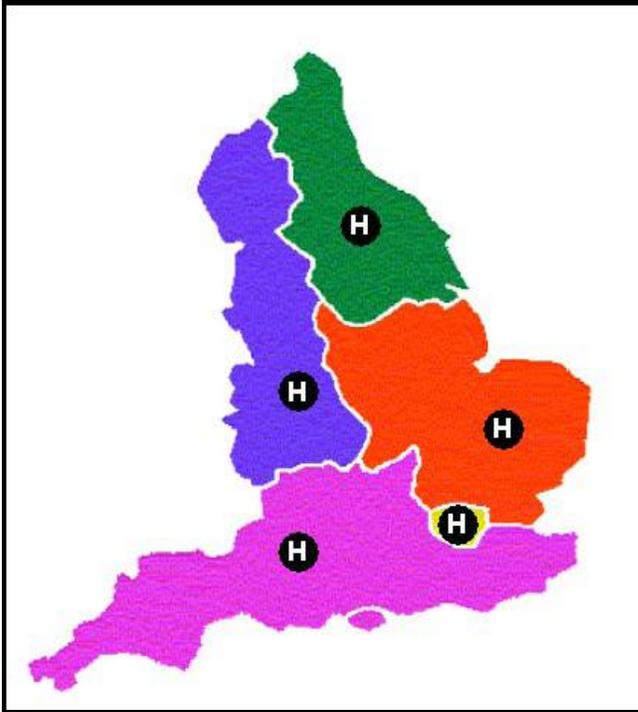


Figure 6- Division of England into Bowel Cancer Screening Programme Hubs (from <http://www.cancerscreening.nhs.uk/bowel/>).

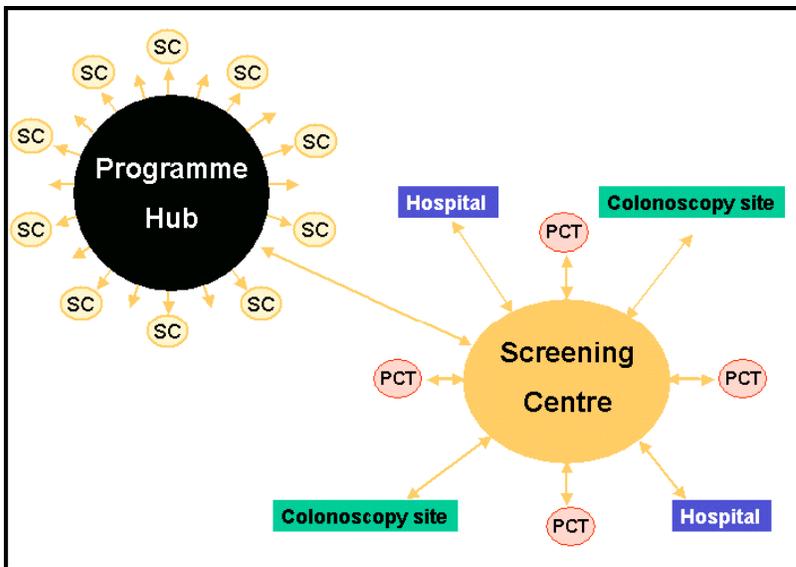


Figure 7- Structure of the NHS Bowel Cancer Screening Programme (from <http://www.cancerscreening.nhs.uk/bowel/>).

Based on data from the pilot studies around 98 in 100 people will receive a normal FOBT result and will be returned to routine screening. They will be invited for bowel cancer screening every two years if still within the eligible age range.

Around 2 in 100 people will receive an abnormal result. They will be referred for further investigation and usually offered a colonoscopy. Around 40-50% of patients who go onto to have colonoscopy will be found to have one or more adenomas. Around 10% will be found to have bowel cancer. This is demonstrated in figure 8.

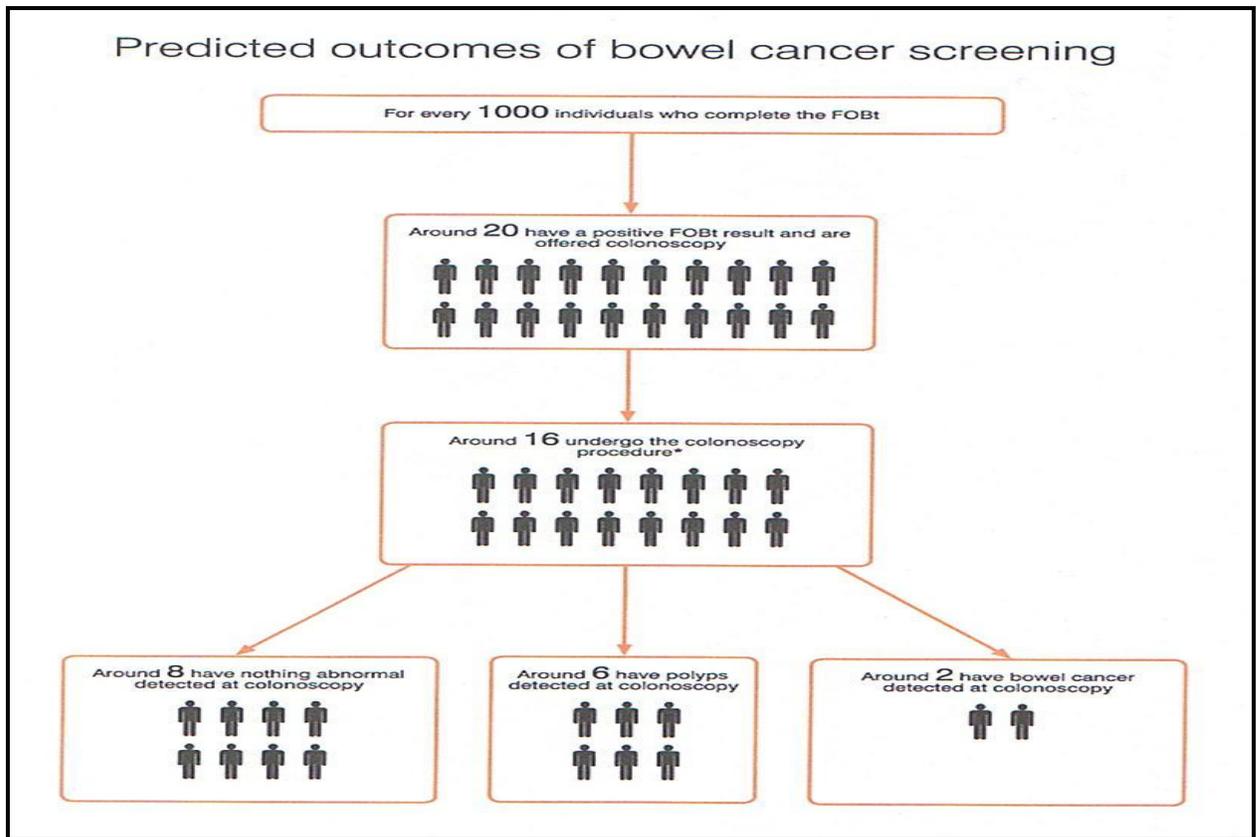


Figure 8- Schematic illustration of predicted outcomes of Bowel Cancer Screening (from <http://www.cancerscreening.nhs.uk/bowel/#screening-work>)

Summary

1. Colorectal cancer is a common disease which imposes a significant burden on society, both in health terms and economic terms.
2. Great advances in understanding of the natural history of colorectal cancer have been made over the last 40 years.
3. This has led to the acceptance of the 'adenoma-carcinoma' sequence being the origin for most colorectal cancers.
4. Fortunately the transition of adenomas to cancer takes place over many years and this provides the ideal opportunity for a screening programme to detect and remove such lesions before they become malignant.
5. Larger adenomas and colorectal cancers tend to bleed intermittently. This means that the detection of blood in the faeces (using a faecal occult blood test (FOBT)) may allow their detection. However FOBT testing only detects around 50% of such lesions due to the intermittent nature of the bleeding.
6. Early diagnosis of colorectal cancer confers significant survival advantages.
7. Three large randomised control trials of biennial FOB testing have demonstrated a reduction in mortality from colorectal cancer of 13-21%. One of these studies demonstrated a 17% reduction in colorectal cancer incidence after 18 years of follow up.
8. On the basis of these large trials, the NHS Bowel Cancer Screening Programme (NHS BCSP) invites men and women aged 60-69 years to enter a biennial FOB testing programme with colonoscopy recommended if the FOB test is positive.
9. The NHS BCSP aims to detect cancers at an earlier stage and detect and remove adenomas.

2.2.0- Detection of Neoplasia in the NHS Bowel Cancer Screening Programme

2.2.1- Adenoma detection rate and other performance indicators in the NHS Bowel Cancer Screening Programme.

The degree of success with which a colonoscopy detects adenomas and carcinomas is a marker of the quality of that colonoscopy and depends on a wide range of factors. High quality colonoscopy is important, particularly within a screening programme, to maximise diagnostic yield, minimise harm to the patient and optimise the benefit to the patient undergoing screening (Valori et al 2010). Being able to measure the quality of a colonoscopy (or colonoscopist) is important for monitoring standards and allowing continuous improvement of the screening programme (Faigel et al 2006). This section of the literature review will examine the evidence available on adenoma detection rate and in particular examine its role as an indicator of performance. The other factors which may or may not influence adenoma detection rate will also be examined.

Adenoma detection rate

Adenoma detection rate (ADR) is a measure of the frequency at which adenomas are detected at colonoscopy. Usually ADR is described as the proportion of patients in whom one or more histologically proven adenomas are found in a defined group of patients in a defined period of time (Church 2008). ADR is usually expressed as a percentage (e.g. 47%) or as a proportion (0.47). For example if colonoscopy is performed on 100 patients by a single colonoscopist in a one year period and one or more adenomas are found in 40 of these patients, the adenoma detection rate for that colonoscopist in that one year period would be 40% (0.4). Occasionally it is expressed as the total number of adenomas per patient. This may be more relevant in populations with high polyp prevalence. In the example above, if a total of 60 polyps were found in those 40 patients who had one or more adenomas, the total number of adenomas per patient would be 0.6. There is no evidence available to inform which of these two measures of adenoma detection rate

should be used to compare individual colonoscopists, however the first definition (number of patients in whom at least one or more adenomas is found) is far more widely used. ADR requires that the adenoma be histologically confirmed. Thus it relies not only on the adenoma being detected in the first place but also removed, retrieved and analysed in a laboratory by a pathologist. In this way ADR differs from polyp detection rate (PDR) which simply requires a polyp (of any nature) to be macroscopically identified at colonoscopy.

A number of studies have demonstrated variable adenoma detection rates amongst colonoscopists (Atkin et al 2004; Barclay et al 2006; Millan et al 2008; Bretagne et al 2010). In one of these studies, which looked at six experienced colorectal surgeons (each had performed more than 1000 procedures) at the Cleveland Clinic, Ohio; the adenoma detection rates amongst the surgeons varied from 14.2% to 27.4% (Millan et al 2008). This was independent of completion rate which was uniformly greater than 95%. Although this was a small study it demonstrates variability in ADR and raises questions as to why this should be the case.

The following factors have been suggested as contributing to variation in adenoma detection, the magnitude of the potential effect of these factors is shown in table 11.

- Endoscopist characteristics
 - A study of 9 colonoscopists at the Indiana University Hospital reviewed 10,034 colonoscopies (Chen et al 2007). Multivariable analysis indicated that increasing age and male gender of the patient were associated with increased adenoma detection rate. When these factors were controlled for in a further multivariable analysis, there were significant differences in adenoma detection rate ($p < 0.0001$) among the colonoscopists (range 14%-46%). All endoscopists had a caecal intubation rate of 93% or higher but had a wide range of previous experience in clinical practice on entering the trial (mean number of years 8.8, range 0-25). The impact of previous experience and intubation rate was not examined in this study but the influence of the individual colonoscopist was demonstrated.

- Technical factors

The techniques used to perform colonoscopy can have an important impact on adenoma detection rate. These factors include:

- Withdrawal time greater than 6 minutes (Barclay et al 2006)
- Position change during colonoscopy (East 2007a; East 2011)
- Use of an antispasmodic agent (East 2007b)
 - One study has suggested premedication with Buscopan (Hyoscine Butylbromide) can increase adenoma detection though the effect was small, non-significant and confined to individuals with marked colonic spasm (Lee 2010). A study from St Marks (Saunders 1996) suggested Buscopan could decrease colonoscope insertion time, a further study from the same institution showed that Buscopan could increase the amount of colonic mucosa that can be inspected (East 2009).
- Re-examining folds and flexures (Rex 2000)
- Rectal retroflexion (Hanson et al 2002)
- Quality of bowel preparation (Harewood et al 2003)
- Time of day (Sanaka et al 2009; Chan et al 2009)
 - A higher ADR is reported in the morning than the afternoon, possibly due to changes in the quality of bowel preparation or endoscopist fatigue. Two US studies have demonstrated that polyp detection decreases in afternoon compared with morning colonoscopies and with each subsequent hour of the day (Sanaka 2009, Chan 2009). A recent single centre US study (Long 2011) of 20 colonoscopists has observed a similar phenomenon of declining polyp detection toward the end of an endoscopist's shift.

- Endoscopic equipment
 - Use of high definition (HD) colonoscopes and narrow band imaging to augment adenoma detection rate have not been shown to improve detection rates (Rex et al 2007; East 2008b). Both these studies were performed by operators with very high baseline adenoma detection rates which may have masked any advantage due to sample size due to high detection rates in the ‘control’ arm. Individual trials of variable stiffness colonoscopes have shown mixed outcomes in improving caecal intubation rate. However a meta-analysis has suggested an association with higher intubation rate (Othman et al 2009) and possibly increased patient comfort. There is no evidence at present that the manufacturer of the endoscopic equipment in use affects adenoma detection rate.

Factor	Degree of effect	Reference
Withdrawal time greater than 6 minutes	ADR 11.8% vs. 28.3%, p=0.001	Barclay 2005
Position change during colonoscopy	ADR positively correlated with an improved distension score (correlation coefficient, 0.12; p< .001).	East 2008a, 2011
Use of an antispasmodic agent	Mean number of polyps in patients with high colonic spasm score in hyoscine group 1.2 vs. 0.41 in the placebo group, p=0.060	Lee JM 2010
Rectal retroflexion	1% increase in ADR	Hanson 2002
Quality of bowel preparation	Odds ratio for polyp detection 1.46 (1.11-1.93) for high quality vs. low quality preparation	Froelich 2005
Time of day	27% more polyps earlier in the day than later Morning ADR- 29.3% Afternoon ADR 25.3% (p=0.008)	Chan 2009 Sanaka 2009
High definition	1.34 small (<6mm) adenomas vs. 0.83 in the control group (p=0.03)	East 2008b
Chromendoscopy	33% in dye spray group vs. 25% in control group p<0.001	Brooker 2002
Narrow Band Imaging	No different to white light in Rex 2007, Increase in total number of adenomas in Inoue 2008.	Rex 2007 Inoue 2008

Table 11- Technical colonoscopy factors affecting ADR and the potential magnitude of effect.

Limitations of using ADR as the primary indicator of colonic performance exist. ADR depends on the underlying prevalence of adenomas in the population being colonoscoped. It also varies depending on the indication for the colonoscopy (Millan 2008) and the age and sex of the patient (Rex 1993). Care is required therefore, when comparing the ADRs of different colonoscopists as the populations they are investigating may differ.

As mentioned, many factors impact upon adenoma detection rate during colonoscopy. Each will be considered below.

Colonoscopy withdrawal time

Colonoscopy withdrawal time (CWT) is the length of time the colonoscopist spends withdrawing the colonoscope from the colon once the caecum has been reached. It is assumed that during this phase of the examination detailed mucosal inspection takes place and abnormalities, subtle or otherwise, are identified.

CWT has been shown to positively correlate with an individual colonoscopist's polyp and adenoma detection rate (especially for polyps smaller than 5 mm (Simmons et al 2006)). In a study by Barclay et al (2006) of 2053 screening colonoscopies, colonoscopists with a mean CWT of less than 6 minutes detected less neoplasia than those with mean CWT greater than 6 minutes (11.8% vs. 28.3%, $p=0.001$). Similarly, advanced neoplasia was detected less frequently (2.6% vs. 6.4%, $p=0.005$). In this trial CWT was measured in both procedures in which no polyps were discovered and procedures in which 'a polyp or mass was manipulated'. Encountering pathology and possible removal of the pathology (polypectomy) during colonoscopy will inevitably prolong withdrawal time. A more accurate reflection of the duration of mucosal inspection should therefore be drawn from analysing CWT during 'normal' colonoscopies. The figures quoted from this study refer to CWT in procedures in which no pathology was encountered.

The same authors then went on to impose a minimum withdrawal time of 8 minutes in their unit. They used the data presented in their original study as baseline (Barclay et al 2008). During the subsequent 13 months in which 2325 screening colonoscopies were performed, a minimum withdrawal time of 8 minutes and optimal withdrawal technique were employed. An increase in ADR from 23.5% to 34.7% ($p<0.0001$) was seen. The increase in advanced adenoma detection rate was not significant (5.5% in the baseline group vs. 6.3% in the post-intervention group ($p=0.18$)). There were however, positive correlations between CWT in procedures without polyp removal and adenoma, and advanced adenoma detection rates ($r_s=0.64$, $p=0.03$ and $r_s=0.53$, $p=0.07$). This study is

limited by being an observational study in which the colonoscopists were aware of the intervention. It suggests a modest benefit from imposing a minimum withdrawal time.

Sawhney et al (2008) did not find an increase in polyp detection rate (PDR) when they studied the effect of a policy of a minimum CWT of 7 minutes in their institution. In this study 42 colonoscopists performed 23,910 colonoscopies. At the start of the study period there was 65% compliance with a 7 minute CWT. At the end of the study period, compliance had risen to nearly 100%, however no significant increase in polyp detection rate was observed. The absence of an increase in PDR in this study may have been because of the high baseline PDR (48%) amongst the colonoscopists. The authors suggest that CWT does not in itself affect lesion detection rate but rather, it is a marker of meticulousness of the colonoscopist and the quality of their technique.

In the NHS Bowel Cancer Screening Programme, which also has a high baseline ADR, a small study presented as an abstract compared mean CWT for 5 colonoscopists with their respective adenoma detection rates. A significant positive correlation was found (Spearman $r=0.97$, $p=0.02$) (Nylander et al 2008).

CWT has not been shown to correlate with longer term clinical outcomes such as interval cancer rate (Gellad et al 2010). However, baseline withdrawal time was calculated from only 304 procedures where no polyps were detected. The mean withdrawal time at baseline (calculated per medical centre) may have been too high (12 minutes) to demonstrate variation which is associated with lower withdrawal times.

In summary, the evidence suggests that a minimum CWT of 6 to 8 minutes is associated with an increased ADR, especially for colonoscopists with low baseline adenoma detection rates and for the detection of small lesions.

The concept of having an arbitrary cut off for minimum CWT may help with setting minimum standards. It is likely however, that a linear relationship between CWT and ADR exists (Rex 2002). No plateau effect has been observed, however there must be a point at which ADR ceases to increase with increased CWT as there is a finite number of adenomas in each colon. Thus the optimal CWT is one which allows complete inspection

of the colonic mucosa and maximizes ADR without prolonging the examination such that it is uncomfortable for the patient or uneconomic in terms of allocation of resources.

Caecal intubation rate

Caecal intubation rate (CIR) was, for many years, the most frequently used marker of colonoscopic performance. Opinion recently has favoured outcome related quality indicators (such as ADR) because CIR is felt to be a measure solely of the colonoscopists ability to reach the caecum rather than their ability to perform a quality examination in terms of mucosal inspection. CIR has been shown to be independent of ADR as an indicator of quality (Millan et al 2008).

Caecal intubation is defined as reaching the caecal pole during colonoscopy. Identification of the caecal landmarks (ileocaecal valve, appendiceal orifice and the tri-radiate fold) are essential. For quality monitoring purposes this should be documented by taking a photograph of the caecal pole. Caecal intubation rates in the major trials of colorectal cancer screening have consistently been above 95%. Therefore, the use of CIR as a discriminator of quality of colonoscopy within a screening programme may be limited.

A large retrospective study (of contemporaneously gathered data) reviewed the details of 17,100 colonoscopies performed by 45 colonoscopists (Harewood et al 2005). The mean CIR was 93.9% (SD 2.9%). Table 12 shows the factors tested for correlation with CIR.

Variable	Correlation	Statistical significance
Extubation time (CWT) (average withdrawal time 6.5 minutes (SD2.8min))	No correlation between increasing CWT and increasing CIR	r=0.12 p=0.41
Gender of endoscopists (female 12.8%, male 87.2%)	No difference in CIR between males (94.2%) and females (92.8%)	p=0.40
Experience of the colonoscopist (mean experience=10.1 years (SD 7.4))	Weak correlation between increasing volume and increasing CIR	r=0.11 p=0.46
Annual volume of colonoscopy per endoscopist (mean volume=363.8 procedures (SD 176.0))	Increasing experience correlates with improving CIR >9 years experience is a predictor of CIR	r=0.35, p=0.017 OR 3.43 95% CI 1.03-12.29 p=0.04
	For junior faculty members (≤5 years experience)- higher volume predicts CIR Within this group- CIR if volume >200/year= 92.5% CIR if volume <200/year= 88.5%	OR 12.0 (95% CI 1.03-33.3) P=0.04
Insertion time (average insertion time= 9.5 minutes (SD 2.8))	Correlation between declining insertion time and increasing CIR	r=0.36 p=0.013
	Correlation between increasing endoscopist experience and declining insertion time	r=0.47 p=0.0008
Age of endoscopists (mean age= 44 years (SD 7.0))	Correlation between increasing age and increasing CIR	r=0.37 p=0.011
	Strong correlation between age and experience	r=0.92 p<0.0001

Table 12- Factors associated with (green) and not associated with (red) caecal intubation rate: findings from an analysis of 45 colonoscopists (Harewood et al 2005).

The main conclusions of this study were a direct correlation between endoscopists experience and caecal intubation. The author recommends that inexperienced colonoscopists need to perform at least 200 procedures per year to maintain adequate CIR. The study is limited by being retrospective in nature, however the data were gathered in 'real-time'. Another limitation was that confirmation of caecal intubation relied on the judgement of the endoscopist. It is known that there is high intraobserver variability amongst endoscopists in recognising the anatomical landmarks in the caecum (Marshall et al 1996).

Patient specific factors may also impact upon caecal intubation (Waye 1991). These include:

- Age
- Gender (Saunders et al 1996)
- Adequacy of bowel preparation
- History of pelvic surgery

The frequency of patients with these characteristics may vary within different study populations, these variables should be controlled for in trials examining caecal intubation rate.

Complete examination of the colon to the caecum is important as a proportion of colorectal neoplasms may be found in the proximal colon. More careful inspection of the right side is increasingly important in the light of studies demonstrating that screening colonoscopy does not reduce mortality from right sided cancer. A Canadian community based study examined the protective benefit against colorectal cancer of having had a colonoscopy (Baxter et al 2009). Patients who were diagnosed with colorectal cancer were 31% less likely to have had a colonoscopy in the preceding 6 months than people who were not diagnosed with colon cancer. Complete colonoscopy was strongly associated with fewer deaths from left sided colorectal (adjusted conditional OR 0.33 (95% CI 0.28-0.39)) but not from right sided colorectal cancer (OR 0.99 (95 % CI 0.86-

1.14)). The quality of the colonoscopists in this trial, however, is not known (69% were generalists or surgeons) and the quality of the procedures (including extent) cannot be verified. More recently, data from the German studies (Brenner 2011) have suggested that colonoscopy is protective against right and left sided colorectal cancer with adjusted odds ratio for left sided cancer of 0.44 (CI, 0.35 to 0.55), and right sided cancer 0.16 (CI, 0.12 to 0.20) if colonoscopy had been performed in the preceding 10 years. Overall, colonoscopy in the preceding 10 years was associated with a 77% reduction in the risk of colorectal cancer (95% CI 73-81%)

Another contributing factor to the lack of protection from right sided colorectal cancer by colonoscopy may be the different natural history of right sided cancers. There is increasing awareness of the heightened malignant potential of serrated polyps/adenomas (SSP(A)s) which tend to be found proximally and are difficult to detect at colonoscopy. Such large (>1cm), proximal polyps may be as common as or more common than large adenomas. (East et al 2008c; Spring et al 2006; East et al 2008d)

Bowel preparation

Prior to performing colonoscopy it is necessary to purge the bowel to remove faecal matter using laxatives and other purgative agents. This allows inspection of the mucosa. Residual faecal matter not cleared by the bowel preparation may be removed during colonoscopy by washing or suction; however, if it is unable to be removed it may obscure the endoscopist's view of the mucosa and contribute to the risk of missing lesions.

Poor preparation increases intubation time and reduces detection of small and large adenomas (Harewood et al 2003; Froelich et al 2005). In addition, the quality of bowel preparation is an indicator of quality of the endoscopy unit itself as the logistics of getting the correct bowel preparation to the patient with adequate instructions requires infrastructure and organization.

US guidelines state that the quality of bowel preparation should be recorded for each procedure (Rex et al 2006). At present there is no standard system for measuring adequacy of bowel preparation. Most scales in use are based on the amount of

intraluminal contents remaining and use terms such as “excellent, good, poor or inadequate”. These terms lack standard definitions.

The U.S. Multi-Society Taskforce on Colorectal Cancer has defined an adequate bowel preparation as allowing the detection of polyps 5mm or larger in size (Rec et al 2002).

Two recently described and validated scales for measuring quality of bowel preparation have been described. Both score the quality of preparation in each colonic segment. The Boston Bowel Preparation Scale (BBPS) has been shown to have good intra-observer reliability (weighted kappa= 0.77 (95% CI, 0.66-0.87)) amongst 22 colonoscopists. It has also been shown to be associated with endoscopic findings such as ADR and other variables such as CWT. It is applied after the endoscopist has performed any additional cleansing manoeuvres, which makes it more clinically relevant (Lai et al 2009). The Ottawa Bowel Preparation Scale also demonstrates intraobserver consistency (kappa ICC of 0.94 (95% CI, 0.91-0.96) but has not been demonstrated to be positively correlated with colonoscopy findings (Rostom et al 2004).

Patient comfort and use of sedation

Multiple factors may be associated with increased patient discomfort during colonoscopy (Park et al 2007).

- Procedure
 - Longer Duration
 - Technically difficult procedure
 - Use of air instead of CO₂ insufflation (Sumanac et al 2002)
 - Non-use of variable stiffness colonoscopes (Brooker et al 2001)
 - Use of transparent caps (Sata et al 2008)
- Patient
 - Younger age

- Female sex
- Previous pelvic surgery
- Diagnosis of IBD
- Low BMI
- Colonoscopist
 - Lesser experience
- Sedation
 - Type
 - Amount

As with quality of bowel preparation, no validated scoring system for patient comfort is widely in use. Patient comfort during colonoscopy is important for a number of reasons. First, in order to ensure a satisfactory experience for the patient colonoscopy should not be a painful procedure. Second, to ensure the patient is not deterred from having another colonoscopy as repeated procedures may be necessary within a screening or surveillance programme. Third, recent studies have suggested that deeper sedation may improve adenoma detection rate (Radaelli et al 2008; Hoda et al 2009). It may be concluded that a calm, unrushed environment in which the patient is deeply sedated and the colonoscopist is able to concentrate fully on the procedure itself allows more careful mucosal examination. An awake, comfortable patient should provide a similar environment with the added benefit of enabling position changes and continuous feedback from the patient. Patient comfort and sedation practice are intimately linked. Conscious sedation is the recommended approach to sedation in the UK (Guidelines on Safety and Sedation During Endoscopic Procedures, BSG 1991). This acknowledges the trade-off between minimising patient discomfort and the increased risk of complications associated with deeper sedation (especially cardiorespiratory complications) (Scoping Our Practice, NCEPOD, 2004). Use of sedation however, may affect adenoma detection rate. An

Italian prospective review of 12835 patients undergoing colonoscopy found that use of sedation was significantly associated with finding one or more polyps (use of sedation vs no sedation odds ratio 1.17 95% CI 1.07-1.23) (Radaelli et al 2008). Two US studies have demonstrated higher ADR in more deeply sedated patients (Hoda et al 2009; Wang et al 2010).

Increasingly, sedation free colonoscopy is being performed, with or without the use of nitrous oxide and air. A US review of 578 patients choosing to undergo colonoscopy without sedation found that 85% of men and 67% of women were able to tolerate the procedure without requesting analgesia or sedation. Caecal intubation rates were maintained regardless of the need for sedation. 97.4% of patients undergoing sedation free colonoscopy were satisfied with their comfort level and would undergo the procedure again without sedation (Petrini et al 2009). This may be seen as a marker of colonoscopic expertise, requiring technical excellence to negotiate the colon without causing discomfort. However, minimising sedation use should not compromise the quality of the colonoscopy in terms of mucosal inspection, CWT and lesion detection.

Rectal retroflexion

Rectal retroflexion is the technique of inspecting the distal rectum and anus from above by placing the colonoscope in a “J” position. It overcomes the difficulty inspecting the distal rectum with a forward viewing endoscope. A study of retroflexion during flexible sigmoidoscopy estimated an absolute 1% increase in ADR when retroflexion is routinely performed, without any increase in patient discomfort (Hanson et al 2002).

A more recent US study has suggested a much lower yield for neoplasia with retroversion (Saad et al 2008). 1502 patients underwent colonoscopy with retroflexion successfully performed in 1411 (93.1%). Only 7 of 40 polyps were seen at retroflexion that were not seen with careful forward viewing examination of the rectum. 6 of these 7 polyps were metaplastic and 1 was a sessile tubular adenoma. Retroflexion in the rectum can be associated with discomfort and perforation and is therefore not routinely recommended

by US Guidelines. In the NHS BCSP however, retroflexion is recommended. Further studies of the need for rectal retroversion are required.

Incidence of interval lesions

The aim of the NHS BCSP is to detect colorectal cancers at an earlier stage or to prevent colorectal cancer by removing adenomas. If a cancer or an adenoma is present but is not detected by colonoscopy it constitutes a missed lesion. Missed lesions only become apparent if the patient becomes symptomatic and requires repeat investigation or if a lesion is found during a surveillance colonoscopy within a timeframe such that it was likely to have been present during the previous investigation. These cancers are collectively termed 'post colonoscopy colorectal cancers' (Rabeneck 2010). Interval cancers are lesions detected between screening rounds or following a screening test in a previous round.

Early studies of colorectal cancer screening in the 1990`s indicated that colonoscopy and polypectomy prevented 76% to 90% of interval cancers (cancers that are found between scheduled screening episodes) (Winawer et al 1993; Citarda et al 2001; Thiis-Evenson et al 1999), these trials involved close colonoscopic surveillance. More recent trials have suggested a higher rate of interval cancers than found in the earlier studies (Schatzkin et al 2000; Alberts et al 2000; Robertson et al 2005). This suggests that colonoscopy and polypectomy is not as protective against colorectal cancer as previously thought. An analysis of individual cases in one of the aforementioned trials (Pabby et al 2005) suggests that over half of interval cancers were either missed or occurred at sites of previous adenomas. A retrospective study of interval cancers (defined as cancers being found within 5 years of a complete colonoscopy) in an American screening programme found that 27% of the interval cancers developed in segments of bowel in which polypectomy had previously been performed (Farrar et al 2006), suggesting incomplete resection of the adenoma at index colonoscopy, the remaining 73% of lesions may have been missed all together.

A number of recent Canadian studies have suggested that colonoscopy is poor at detecting right sided lesions and subsequently confers less protection against right sided cancer (Singh et al 2006; Baxter et al 2009).

Baxter (2009) performed a community based study in Canada which showed that colonoscopy was associated with a reduction in risk of dying from left sided colon cancer (adjusted conditional OR, 0.33 (CI, 0.28 to 0.39)) but not right sided cancer (adjusted conditional OR, 0.99 (CI, 0.86 to 1.14)). This study has been criticised as the competency of the colonoscopists was not known, many were community practitioners for whom no data on colonoscopic quality were available. However, a follow on study from the same group has shown an inverse relationship between increasing colonoscopic quality in terms of caecal intubation and decreasing interval cancer rates (Baxter et al 2011). Similar findings were made in a German study showing reduced rates of left sided advanced adenomas for 10 years following colonoscopy but no reduction in right sided advanced lesions (Brenner et al 2010).

It is possible that some interval lesions are fast-growing cancers, this is supported by the discovery that interval cancers were almost 4 times as likely to display microsatellite instability (a result of loss of function of mismatch repair genes, associated with fast growing tumours) than non-interval cancers (Sawhney et al 2006).

It is known that colonoscopy is not a perfect test and has an inherent “miss-rate” due to a wide range of factors (see 2.2.1). Studies of back to back colonoscopy demonstrate miss rates during colonoscopy of adenomas ≥ 1 cm of 0-6%, 6-9mm of 12-13% and ≤ 5 mm of 15-27% (Hickson et al 1990; Rex et al 1997). A pooled analysis (van Rijn et al 2006) demonstrated a pooled miss rate for polyps of any size of 22% (95% CI: 19-26%; 370/1,650 polyps). Adenoma miss rate by size was, respectively, 2.1% (95% CI: 0.3-7.3%; 2/96 adenomas $>$ or $= 10$ mm), 13% (95% CI: 8.0-18%; 16/124 adenomas 5-10 mm), and 26% (95% CI: 27-35%; 151/587 adenomas 1-5 mm). Subsequent studies using CT colonography have measured the miss rate of adenomas ≥ 1 cm in size by conventional colonoscopy as 12-17% (Pickhardt et al 2004; van Geder et al 2004).

Minimising the interval cancer or miss rate is crucially important to the success of the NHS BCSP as it will contribute significantly to the ability of the screening programme to reduce mortality from colorectal cancer, an outcome by which the success of the programme is likely to be judged. Monitoring the interval cancer rate, therefore, will be an important outcome related quality indicator. Detection of interval cancers will be difficult as few patients will undergo repeat colonoscopy within the programme unless they require surveillance based on findings at index colonoscopy or have a further positive FoBt in a subsequent round. Thus the use of interval cancer rate as a potential marker of quality of colonoscopy in the BCSP will take many years to measure.

Summary

1. Adenoma detection rate is an increasingly important marker of colonoscopic performance and quality.
2. Monitoring colonoscopic performance is important, particularly within the framework of a screening programme, in order to optimize the benefit of the procedure to patients and minimize harm.
3. There is variability in the adenoma detection rates of individual colonoscopists; this can be attributed to a wide range of factors. The functional impact of this may be an association with miss rates of adenomas and cancers.
4. British Society of Gastroenterology and US guidelines recommend that colonoscopists measure their adenoma detection rate.
5. Adenoma detection rate is dependant on a wide range of factors. These factors may relate to the endoscopists, to the patient or to technical aspects of the procedure.
6. Improving adenoma detection rate may reduce interval lesion rate, further research in this area is necessary.
7. Increasing colonoscope withdrawal time (CWT) is probably correlated with increasing adenoma detection rate however this effect may be attenuated if there is a high baseline ADR. CWT may be used as a marker of the quality of an individual colonoscopist's technique.
8. Caecal intubation rate (CIR) is of limited use as a marker of quality as it lacks variation. It may however be used to identify poor performance.
9. Quality of bowel preparation and sedation practices are useful surrogate markers of quality of colonoscopy.
10. A single, universal marker of quality of colonoscopy has not been identified. It is likely that a combination of the markers of quality described above is necessary to cover all aspects of procedure (patient-related markers, operator-related markers and outcome-related markers).

2.3.0- Management of Neoplasia in the NHS Bowel Cancer Screening Programme

2.3.1- 12 month surveillance colonoscopy in patients at high risk of future neoplasia

Evidence supporting the BSG guidelines

Patients who have undergone colonoscopy and polypectomy are at a greater risk than the background population of having further adenomas or colorectal cancer in the future (Winawer et al 2003; Atkin et al 1992; van Stolk et al 1998). The risk of having further adenomas or developing colorectal cancer depends on a number of factors including the number, size and degree of dysplasia of the original adenomas (see below).

For this reason patients who have had polypectomy are often recommended surveillance colonoscopy. The interval between index colonoscopy, first surveillance colonoscopy and subsequent surveillance intervals should depend on the magnitude of the individual patient's risk of having further adenomas or cancer at any particular time interval.

Other considerations such as the age, comorbidity, family history, quality of the index colonoscopy and risk of having missed lesions at the index colonoscopy should also be taken into account.

The reasons for finding further adenomas or colorectal cancer at colonoscopy after a patient has already had colonoscopy and polypectomy (of all detected lesions) are threefold.

- New adenomas or cancers
 - Adenomas develop slowly over many years. If the interval between colonoscopies is short it is less likely that new lesions will have developed. Fast growing flat or depressed lesions, particularly in the right colon may have more of a propensity to grow quickly.

- Missed lesions
 - The miss rate by colonoscopy of adenomas greater than 1cm is up to 6% (van Rijn et al 2006). This may account for lesions found at surveillance colonoscopy.
- Recurrence
 - Incompletely resected adenomas may recur.

The purpose of surveillance colonoscopy therefore is to detect new, missed or recurrent lesions.

Certain subgroups of adenomas have a higher risk of becoming malignant over time. The following features are associated with an increased risk of progression to malignancy (Eide 1986):

- 1cm or greater in size
- Higher grade of dysplasia
- Villous architecture
- Increasing number of adenomas

Adenomas which are 1cm or larger in size and those displaying high grade dysplasia are collectively termed advanced adenomas. Because these polyps have a greater malignant potential, there is an emphasis on detecting and removing advanced lesions during colonoscopic surveillance. The presence of advanced adenomas is also a marker for the presence of other lesions which may have been missed. Incidence of advanced adenomas (or advanced adenomas and colorectal cancer, collectively termed 'advanced neoplasia') is an important outcome measure in trials of colonoscopic surveillance.

Advanced adenomas are often defined differently in the US and English literature. In the US literature adenomas with villous histology are included. This is not practice in England due to the perceived inconsistencies of biopsying adenomas leading to unrepresentative sampling and significant intra-observer variability of histological subtyping (Atkin et al 2002; Constantini et al 2003).

A meta-analysis of advanced adenoma incidence during surveillance colonoscopy in patients with a history of adenomas (Saini et al 2006) showed that patients with 3 or more adenomas at index colonoscopy had a higher risk of having recurrent advanced adenomas at follow up than patients with 1 or 2 adenomas at index (Risk Ratio 2.52, 95% CI 1.07-5.97). Patients with high grade dysplasia at index were also at increased risk (Risk Ratio 1.84, 95% CI 1.06-3.19), as were patients with increasing size of adenoma at index. These results contain data from patients undergoing surveillance at heterogeneous intervals (range 10-48 months) and both definitions of advanced adenoma were included. Only surveillance intervals of 2 years or more were included in the analysis suggesting that the lesions found at follow up may have been new or missed lesions.

In the US National Polyp Study (Winawer et al 1993) (a randomised comparison of different surveillance intervals in 1418 patients with adenomas removed at colonoscopy), the cumulative detection rate of advanced neoplasia (US definition) was 3% in the groups having either 1 or 2 colonoscopies in the 3 years following the index procedure.

In the Danish Funen Adenoma follow-up Study the incidence of advanced adenomas was 5.2% at 2 years and 8.6% at 4 years (Jorgensen et al 1995).

Patients with only 1 or 2 small (<1cm) adenomas are at a much lower risk of developing further adenomas or having adenomas missed at index colonoscopy (Zauber et al 1999; van Stolk et al 1998; Noshirwani et al 2000; Martinez 2001). The risk of these patients subsequently developing colorectal cancer is also low. A study of 751 patients who had had small adenomas removed did not show any increased risk of cancer over 10,000 person-years of follow up (Spencer et al 1984). A study of 1618 patients who underwent rigid sigmoidoscopy and polypectomy of rectosigmoid lesions included a group of 776 patients with small (<1cm) tubular adenomas in which no increase in colorectal cancer was observed compared to the general population (Atkin et al 1992).

Patients with a few, small adenomas do not, therefore, warrant colonoscopic surveillance. If, however, a patient has a high adenoma burden, their risk of having had a lesion missed at index colonoscopy or of developing further adenomas is much higher.

Figure 13 demonstrates the increased risk associated with baseline colonoscopic findings.

Findings at index colonoscopy	Risk of advanced adenoma at follow up	Reference
<p>≥3 adenomas</p> <p>≥1 adenoma displaying HGD</p>	<p>RR 2.52 (95% CI 1.07-5.97) compared to having 1-2 adenomas</p> <p>RR 1.84 (95% CI 1.06-3.19)</p>	<p>Saini et al 1996 (Meta-analysis)</p>
<p>≥5 adenomas</p> <p>≥1 villous adenoma</p> <p>≥1 proximal adenoma</p>	<p>24.1% (SE 2.2)</p> <p>OR 1.28 (95% CI 1.07-1.52)</p> <p>OR 1.68 (95% CI 1.43-1.98)</p>	<p>Martinez et al 2001) (Pooled analysis)</p>
<p>1 adenoma (any size)</p>	<p>1% at first follow up</p>	<p>National Polyp Study (Winawer et al 1993)</p>
<p>Four or more adenomas (any size)</p>	<p>5-fold increase compared to 1 or 2 small adenomas at index</p>	<p>Cleveland Clinic Foundation Adenoma Registry (Noshirwani et al 2000)</p>
<p>Multiple adenomas, at least one of which is ≥1cm</p>	<p>10 –fold increase compared to 1 or 2 small adenomas at index</p>	<p>Cleveland Clinic Foundation Adenoma Registry (Noshirwani et al 2000)</p>
<p>Adenoma larger than 1cm</p>	<p>2.7- fold increase risk of colorectal cancer compared to general population</p>	<p>Lofti AM et al 1986</p>
<p>Multiple adenomas and at least one large (>1cm) adenoma</p>	<p>5-fold increase risk of colorectal cancer compared to general population</p>	<p>Lofti AM et al 1986</p>

Table 13- Findings at baseline colonoscopy associated with advanced neoplasia during surveillance

A recent pooled analysis (Martinez et al 2009) from 8 prospective studies comprising 9167 patients who had undergone colonoscopy and polypectomy showed that 12% of the patients were found to have advanced neoplasia during a median follow up period of 47.2

months. The risk of developing advanced neoplasia was higher in patients with 5 or more baseline adenomas (24.1%, SE 2.2) and adenoma greater than 2cm at baseline (19.3%, SE 1.5). The presence of an adenoma with villous architecture and proximal location were also significantly associated with metachronous advanced adenomas (OR 1.28, (95% CI 1.07-1.52) and OR1.68, (95% CI 1.43-1.98) respectively).

Older age ($p < 0.0001$ for trend) and male sex (OR 1.4, (95% CI 1.19-1.65)) were also significantly associated with metachronous advanced neoplasia. High grade dysplasia in baseline adenoma was not associated with further advanced neoplasia when other polyp characteristics were adjusted for. In the group of patients with multiple or large polyps at baseline colonoscopy, closer colonoscopic surveillance may be indicated. The evidence outlined above forms the basis of the British Society of Gastroenterology guidelines on adenoma surveillance (Atkin et al 2002; Cairns et al 2010). The summary of these guidelines are shown in figure 9.

SURVEILLANCE FOLLOWING ADENOMA REMOVAL

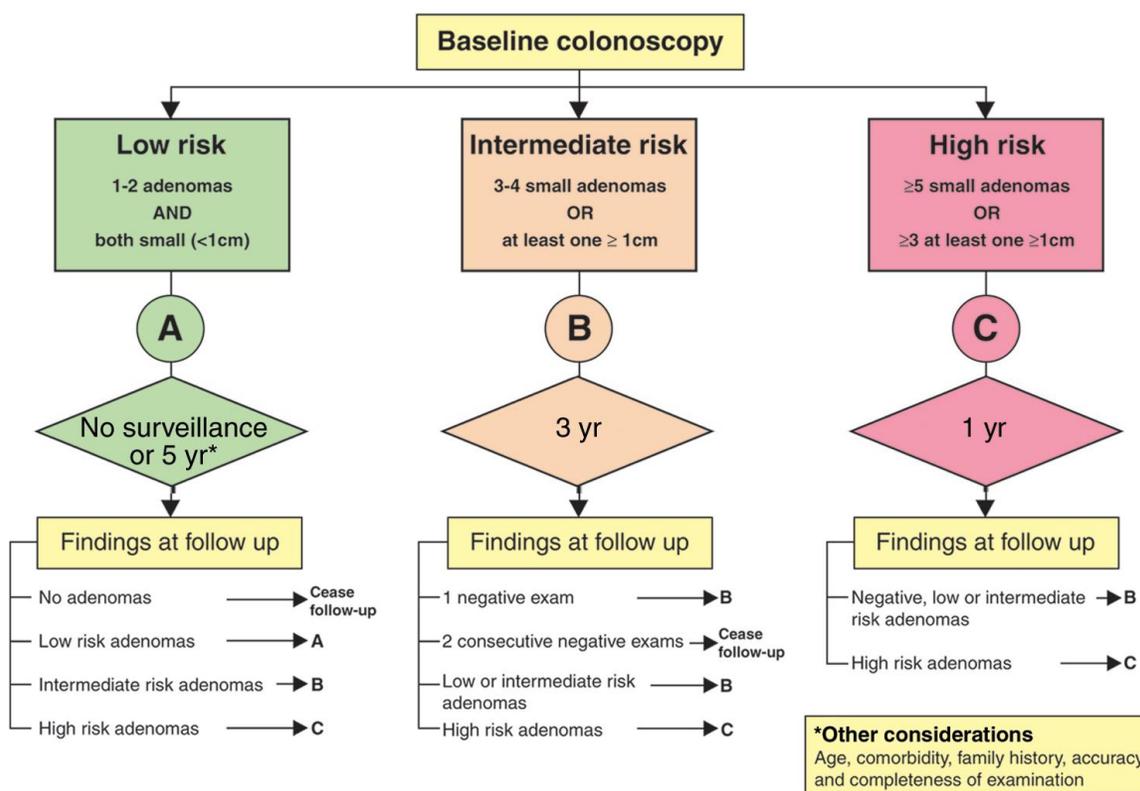


Figure 9- Adenoma surveillance guidelines. BSG (Atkin et al 2002).

These guidelines are widely used in the UK and form the basis of adenoma surveillance in the NHS Bowel Cancer Screening Programme (BCSP). The only variation is that patients with ‘low risk’ polyps in the BCSP return to the biennial FOB testing screening strategy rather than following the guidelines above which would suggest either no further surveillance or a 5 year interval. There are no published data yet on the outcomes of surveillance in the BCSP.

A more recent pooled analysis (de Jonge 2011) of factors predicting the presence of adenomas at surveillance has reinforced the importance of age greater than 60 (pooled relative risk (RR) 1.81, 95% CI), three or more adenomas (RR 1.64), advanced adenoma at index colonoscopy (RR 1.81, 1.13-2.89) and size $\geq 10\text{mm}$ (RR 1.66, 1.32-2.10). Less strong associations were seen for villous adenoma at index (1.21, 0.97-1.45), high grade dysplasia (1.66 (1.26-2.19), proximal location of adenoma at baseline (1.43, 1.30-1.57)

and male gender (RR1.22, 1.12-1.32). Marked variation in study design and substantial heterogeneity between studies included in the pooled analyses were noted.

The European guidelines for quality assurance in colorectal cancer screening and diagnosis make slightly different recommendations for high risk individuals to the BSG guidelines (Segnan et al 2011). The European guidelines recommend an additional clearing colonoscopy at 12 months for individuals with 5 or more adenomas or an adenoma of 2cm or larger due to the substantial risk of missing adenomas with high malignant potential.

Recent studies have examined the effect of dietary and pharmacological interventions on subsequent adenoma development following polypectomy. A US study (Schatzkin et al 2000) of 2079 men and women who had one or more histologically confirmed adenomas removed were randomized to receive either a low-fat, high-fibre diet or to continue on their normal diet. They then underwent colonoscopy at 1 and 4 years. 1905 subjects completed the study. 39.7% and 39.5% had at least one recurrent adenoma during follow up in each group respectively (unadjusted risk ratio 1.00 (95% CI 0.9-1.12)). No protective benefit from this dietary intervention was seen. A trial of high fibre cereal supplements (Alberts et al 2000) did not demonstrate protection against adenoma recurrence in 1303 subjects (47% adenoma recurrence in the high fibre group, 51.2% in the low fibre group (odds ratio 0.88, 95% CI 0.7-1.11, p=0.28)).

The enzyme cyclo-oxygenase 2 (COX-2) is overexpressed in colorectal adenomatous polyps. The PreSAP trial (Arber et al 2006) of Celecoxib (a COX-2 inhibitor) randomized patients who had had one or more adenomas removed to receive either 400mg of Celecoxib daily or placebo. All patients underwent colonoscopy at 1 year and 3 years. The cumulative rate of adenomas detected by year 3 was 33.6% in the celecoxib group and 49.3% in the placebo group (relative risk, 0.64; 95% CI 0.56-0.75; P<0.001). The cumulative rate of advanced adenomas detected through by year 3 was 5.3% in the celecoxib group and 10.4% in the placebo group (relative risk, 0.49; 95% CI 0.33-0.73; P<0.001). Adjudicated serious cardiovascular events occurred in 2.5% of subjects in the

celecoxib group and 1.9% of those in the placebo group (relative risk, 1.30; 95% confidence interval, 0.65 to 2.62).

In a similar trial of Rofecoxib (Baron et al 2006), adenoma recurrence was less frequent for rofecoxib subjects than for those randomized to placebo (41% vs. 55%; $p < 0.001$; relative risk 0.76; 95% confidence interval 0.69-0.83). Rofecoxib also conferred a reduction in risk against advanced adenoma recurrence ($p < 0.001$). In this trial excess serious cardiovascular events and upper gastrointestinal bleeding was observed in the treatment arm. The concerns over cardiovascular and gastrointestinal toxicity have limited the clinical usefulness of COX-2 inhibitors in chemoprevention of recurrent adenomas.

Summary

1. An important aim of colonoscopy is to detect and remove adenoma.
2. Colonoscopy may miss adenomas allowing them to continue to develop.
3. Adenomas may recur following colonoscopy and polypectomy.
4. Despite colonoscopy and polypectomy a patient may go on to develop adenoma and/or colorectal cancer.
5. Certain characteristics of the patient (increasing age, male sex) and of the baseline adenomas (increasing number and size, possibly advancing histological grade and villous architecture) predict adenoma recurrence and likelihood of colorectal cancer following polypectomy.
6. Patients with multiple or large polyps are more likely to benefit from colonoscopic surveillance.
7. The BSG guidelines for adenoma surveillance are incorporated into the NHS Bowel Cancer Screening Programme. Outcomes of 1 year surveillance within the screening programme are not yet known will be reported in this thesis.

2.3.2- Management of large colonic polyps.

When a polyp is detected at colonoscopy, a decision must be made whether to remove the polyp endoscopically, surgically or to not remove it at all.

The following factors will influence the decision:

- Site of the lesion
- Size of the lesion
- Histological nature of the lesion (may require representative biopsies to be taken to assess)
- Age and comorbidities of the patient
- The patients wishes
- Operator experience of endoscopic or surgical management
- Risk of surgical management
- Risk of endoscopic therapy
- Feasibility of endoscopic resection

Endoscopic techniques have progressed to allow the removal of larger and sessile polyps which previously would have necessitated surgical management. New endoscopic techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have facilitated this progress.

Equally, the advent of laparoscopic colorectal surgery has made surgical management of large polyps less invasive and potentially safer than open surgery. The management of large or complex rectal lesions has been advanced by the development of Trans-anal endoscopic Micro-surgery (TEMS) which allows the removal of rectal lesions without a skin incision.

The management of polyps which are shown to have a malignant component on biopsy will not be considered in this literature review as the management of such polyps is

subject to other variables such as depth of invasion and risk of loco-regional spread. The management of presumed large benign polyps will be focused on. Some of these polyps may turn out to have a malignant component once removed.

There is no specific definition for 'large colonic polyp'. Generally, it refers to polyps larger than 2-3cm in size. Polyps larger than 3 cm are sometimes referred to as 'giant polyps'.

Pedunculated polyps (polyps with a definite stalk) are easier and safer to remove than sessile or flat polyps. Therefore the management of sessile lesions will be focused on in this review.

There is no consensus in the literature on the best approach to the management of large colorectal polyps. In experienced hands both approaches seem to be acceptable (Church 2003). Endoscopic management by non experts may be associated with worse outcomes (Brooker et al 2002).

Both surgical and endoscopic approaches to management of large colonic polyps have advantages and disadvantages as shown in table 14.

	Advantages	Disadvantages
Endoscopic management of large adenomas	Avoids the need for general anaesthesia No skin incision Usually performed as a daycase Potentially lower costs incurred En-bloc* resection may be possible	Risk of perforation or bleeding during therapy May require repeated sessions of therapy or site checking Lesion may turn out to be malignant and subsequently require surgery Piecemeal removal may compromise histological analysis Risk of incomplete resection
Surgical management of large adenomas	Complete excision is technically easier Less likely to require repeated episodes of therapy Complete resection specimen is better for pathological analysis	Risk of surgical complications Need for skin incision and subsequent scar Need for general anaesthesia Longer hospital stay Potentially more costly

Table 14-Advantages and disadvantages of endoscopic and surgical management of large polyps.

*En bloc refers to removal of the polyp in one piece, allowing pathological determination of extent of resection. Piecemeal removal of the polyp does not allow the completeness of resection to be determined. There is little evidence available to evaluate the factors outlined in table 14.

No head to head randomized controlled trials of endoscopic versus laparoscopic surgical management of large colonic polyps have been undertaken. Current practice is variable and depends on the local expertise available.

A study from St Mark`s Hospital, UK emphasized the importance of a specialist endoscopist (with experience of managing large polyps) rather than a non-specialist endoscopist assessing such lesions (Brooker et al 2002). In this study two specialist endoscopists attempted endoscopic resection of 80/86 large polyps (≥ 2 cm). Resection was successful in 61/86 (71%) of patients thus avoiding the need for surgery. Non-specialist

endoscopists however, attempted resection of 15 large polyps, 9 of which subsequently required surgical intervention, thus surgery was only avoided in 40%.

A review of 71 patients referred for surgical management of large colonic polyps (average size 24mm, range 10-63mm) demonstrated the importance of colonoscopic reassessment of the polyp by an expert prior to surgery (Lipof et al 2005). In 23/71 (32%) of patients the polyp was removed colonoscopically, obviating the need for surgery.

Endoscopic Management of large colonic polyps

Table 15 displays the available published series of endoscopic management of large colonic polyps. The studies are mostly retrospective in design. The management protocols and inclusion criteria are broadly heterogeneous. However, the same underlying principles of management of large polyps are applied in all studies and the range of data gives a clear overview of the potential benefits and complications associated with endoscopic management of such lesions.

In summary:

- The definition of a large colonic polyp is not consistent. The majority of studies refer to polyps larger than 2 cm in diameter.
- The rate of residual adenoma detected during surveillance varies between 5-54%. The more recent series suggest a rate of residual adenoma or recurrence of around 10%. Comparison of this outcome is limited by variation of definition between studies.
- Bleeding is the most common complication. Delayed bleeding occurs in 0-11% of cases. The most recent, larger series suggest a delayed bleeding rate of 1.5-7%.
- The majority of cases of bleeding can be managed endoscopically without the need for surgery.
- Perforation is a rare complication. It occurs in 0-3% of cases and is almost always associated with attempted resection of a malignant lesion.

- EUS has not been widely used in the assessment of large lesions prior to resection. It's use may improve selection of benign lesions for resection (Hurlstone et al 2005).
- Invasive malignancy is detected in 0-68% of resected polyps. This depends on the assessment process prior to resection. Recent studies in which polyps are assessed endoscopically prior to resection and non lifting lesions excluded suggest 3-5% of large polyps (≥ 2 cm) will contain invasive malignancy and may require surgery.
- Argon plasma coagulation following piecemeal EMR of large sessile polyps reduces recurrence (Zlatanovic et al 1999; Brooker et al 2002).
- The rate of surgery following endoscopic management of large colonic polyps is between 0-37%. The indication is usually either presence of invasive malignancy or incomplete resection. Surgery mandated by a complication such as bleeding or perforation is less common. The most recent series suggest a need for surgery due to recurrence, incomplete resection or malignancy in 4-16% of cases.
- Death associated with endoscopic resection of large colonic polyps has not been reported in any of these series.

US (Winawer et al 2006) and UK guidelines (Cairns et al 2010) recommend surveillance of the polypectomy site following resection of large colonic polyps is undertaken at 3 months. Khashab et al (2009) followed up 136 large polyps (≥ 2 cm). 24 (17.6%) had macroscopic evidence of recurrence at follow up. 18 displayed recurrence at first follow up whilst 6 (4.4%) demonstrated 'late recurrence' – the presence of recurrence despite initially normal surveillance. Negative biopsy of the polypectomy scar was associated with lower recurrence rates in long term follow up. 92 of 94 (97.9%) of normal appearing scars with negative scar biopsies remained free from recurrence at one year. Only 36 of 42 (85.7%, $p=0.005$) polyps with macroscopic or microscopic evidence of recurrence were successfully eradicated at long term follow up. The role of chromendoscopy and endomicroscopy in post polypectomy surveillance is yet to be established.

Endoscopic submucosal dissection (ESD) allows en-bloc resection of large polyps which may lead to lower recurrence rates but is associated with higher complication rates and requires an added level of technical expertise. Zhou et al (2009) reviewed their series of 73 patients undergoing ESD. The mean size of lesions removed was 32.6mm (range 20-85mm). Minor bleeding occurred in all cases. One patient (1/74, 1.4%) had massive bleeding requiring endoscopic therapy. 6/73 patients (8.1%) experienced perforations. All but one settled with conservative management. One patient (1.4%) required surgery due to perforation. En-bloc resection was possible in 69/74 procedures. The overall residue or recurrence rate at one year was 0%.

Surgical Management of large colonic polyps

A retrospective review comparing 2500 endoscopic polypectomies with 58 patients requiring laparoscopic resection for non-endoscopically removable polyps in a single German unit (Hauenschild et al 2009), showed that laparoscopic surgery was a safe and effective approach for managing such polyps. 4 of 58 patients (6.9%) required conversion to open surgery. 5 patients (9.5%) experienced peri-operative complications. Details of endoscopic complications were not presented.

Two US studies including a series of 51 patients referred for laparoscopic colectomy for endoscopically unremovable polyps to the Cleveland clinic in Ohio (Pokala et al 2007; Brozovich et al 2008) warned against the endoscopic management of such lesions. Adenocarcinoma not previously detected at colonoscopy was found in 11 polyps (20%). 5 patients (9.8%) required conversion to open surgery. Mean hospital stay was 3.1 (+/- 1.9) days. 6 surgical complications occurred (17.7%) (1 anastamotic leak, 1 small bowel obstruction, 1 abcess, 2 exacerbations of existing medical conditions).

A comparison between open and laparoscopic resection of colonic polyps from the Cleveland Clinic, Florida (Joo et al 1998) showed definite advantages of laparoscopic over open surgery in terms of post-operative pain, earlier return of bowel function and earlier return to normal function. The limitations of the laparoscopic approach were

longer operation times (although this study is now 11 years old) and shorter resection specimens (long term follow up data was not presented).

Laparoscopic-assisted colonoscopic polypectomy, in which the polyp is located and removed endoscopically but with concurrent laparoscopy allowing mobilization of the colon and close inspection of the serosal surface, has been suggested to minimize the risk of complications (Hensma et al 2009). The use of this approach has not become widespread.

Transanal endoscopic microsurgery (TEMS) is a surgical approach to remove large rectal lesions. A number of retrospective and prospective case series have demonstrated recurrence rates of 0-19% and complication rates of 2-21%. These figures are comparable to endoscopic management (Neary et al 2003; Middleton et al 2005). TEMS has never been compared to endoscopic mucosal resection of large rectal adenomas in a large multicenter randomized controlled trial, however, such a trial is currently underway (TREND-study) (van der Broek et al 2009).

The cost implications of endoscopic versus laparoscopic management of large colonic polyps have been estimated in a number of studies. Swan et al (2009) reviewed 174 patients referred to a tertiary unit for management of 193 polyps. 173 lesions were excised by EMR. 11 patients went straight to surgery due to suspicion of malignancy and a further 7 required surgery due to incomplete resection or malignancy in the resected specimen. They assumed that the 157 of 168 patients with benign lesions successfully treated endoscopically had avoided the need for surgery and on this basis they calculated a cost saving of \$6990 (US) per patient.

Brooker et al (2002) estimated the mean cost per patient of endoscopic management by a specialist endoscopist as £1500. Using available data on 16 patients in their study who required surgery they estimated the mean cost of surgical management of benign large colorectal polyps as £5260.

Detection and Management of Colorectal Neoplasia in the NHS Bowel Cancer Screening Programme

Year	Lead Author	Country	Size	Number of Polyps	Morphology (Sessile or Pedunculated)	Rate of residual adenoma at initial surveillance	Bleeding	Perforation	Presence of malignancy in resected polyps	EUS used	Need for surgery	Deaths
1986	Bedogni	Italy	≥3cm	66 (36 sessile)	Mixed	6/36 (16.7%)	2/66 (3%)	0	N/R	No	0	0
1992	Walsh	USA	≥2cm	132	Sessile	28%	2%	1%	17%	No	27% (malignancy)	0
1996	Binmoeller	Germany	≥3cm	129	Sessile	16%	9%	0	12%	No	1 residual tumour, 1 malignancy	0
1996	Kanamori	Japan	≥3cm	25	Sessile	0	3/33 (9%)	0	16%	No	0	0
1999	Zlatanic	USA	≥2cm	77	Sessile	50%	5%	1/77	0	No	0	0
2000	Iishi	Japan	≥2cm	56	Sessile	54%	0	0	68%	No	4 residual tumour 1 bleeding	0
2001	Dell'Abate	Italy	≥3cm	104 (35 sessile)	Mixed	3/63 (5%)	1/104 (1%)	0	27/104 (26%)	No	2 synch Ca, 1 recurrence HGD	0
2002	Brooker	UK	≥2cm	130	Sessile	9/80 (11%) (benign polyps)	4%	0	14%	No	21 (malignancy) 24 (benign polyps)	0
2002	Morton	USA	≥2cm	131 (116 sessile)	Mixed	41/82 (50%)	14/131 (11%)	0	4/131 (3%)	No	1 (malignancy)	0
2002	Stergiou	Germany	≥3cm	68 (41 sessile)	Mixed	12/68 (28%)	3/68 (4%)	0	7/68 (10%)	yes	1 (malignancy)	0
2003	Higaki	Japan	≥2cm	24	Sessile	4/23 (22%)	N/R	N/R	1/24 (4%)	No	0	0
2003	Regula	Poland	≥18mm	82	Sessile	14%	2%	0	7/82 (9%)	No	2 malignancy 2 recurrence	0
2003	Doniec	Germany	≥3cm	186 (141 sessile)	Mixed	7/186 (4%)	3/104 (2%)	1 (cancer)	27/104 (26%)	No	1 (bleeding) 1 (perforation) 9 (cancer)	0
2003	Church	USA	≥2cm	311 (263 managed endoscopically, 48 surgically)	Mixed (238 flat/sessile)	44/201 (22%)	17/311	0	19/311 (6.1%)	No	18 (recurrence or malignancy)	0

Year	Author	Country	Size	Number of Polyps	Morphology (Sessile or Pedunculated)	Rate of residual adenoma at initial surveillance	Bleeding	Perforation	Presence of malignancy in resected polyps	EUS used	Need for surgery	Deaths
2004	Conio	It/Fr	≥2cm	139	Sessile	21/96 (22%)	0	0	17/136 (13%)	No	10 (malignancy)	0
2005	Hurlstone	UK	≥18mm	83	Sessile	5/62 (8%)	0	0	0	Yes	1 (non lifting)	0
2006	Boix	Spain	≥4cm	74	Sessile	5/54 (9%)	10/74 ?timing	0	12/74 (16.2%)	No	12 (16%) malignancy	0
2007	Arebi	UK	≥2cm	161	Sessile	60/146 (40%)	7 (5.7%)	0	5.5%	No	3 (recurrence) 1 (Incomplete resection) 3 (malignancy)	0
2008	Al-Kawas (Abstract)	USA	≥2cm	96 (76 sessile)	Mixed	10/96 (10.4%)	7/96 (7%)	3/96 (3%)	18/96 (18.8%)	No	2 (perforation) 8 (malignancy) 3 (incomplete resection)	0
2009	Khashab	USA	≥2cm	136	Sessile	24/136 (17.6%)	6/136 (4.5%)	0	1 (0.7%)	No	0	0
2009	Caputi Iambreghi	Italy	≥2cm	151 (72 sessile)	Mixed	9/151 (6.9%)	2/151 (1.5%)	3/151 (2.3%) all malignant	5/147 (3.4%)	No	3 (bleeding) 2 (Perforation) 5 (malignancy)	0
2009	Swann	Australia	≥1cm	193 (186 sessile)	Mixed	10.5%	7/193 (3.7%)	0	9/193 (3%)	No	5 (malignancy) 2 (incomplete resection) 11 (lesion not amenable to EMR)	0
2010	Ferrara	Italy	≥2cm	182	Sessile	12/172 (6.9%)	22 (12.4%)	2 (1.1%)	13 (7.3%)	No	13/157 (8.3%)	0
2011	Moss	Australia	≥2cm	479	Sessile	20.4%	14/476 (2.9%) admitted, 6 required endo, 1 surgery	6/476 (1.3%)	33/476 (6.9%)	No	78/476 (16.3%)	0

Table 15- Published series of endoscopic management of large colonic polyps

Summary

1. Historically, large colonic polyps were managed by open surgical resection.
2. Modern endoscopic techniques such as EMR and ESD make removal of large colonic polyps possible. Endoscopic management has a number of advantages over surgical management.
3. Advances in laparoscopic surgery mean that surgery for large polyps is less invasive and still has a role in the management of such lesions.
4. Current management of large colonic polyps depends on available local expertise.
5. Ideally, large polyps should be assessed by an expert endoscopist and resection only attempted if malignancy is not suspected.
6. Endoscopic resection of large polyps is reasonably safe and effective in expert hands. Bleeding is the most common complication but rarely requires surgical intervention. The risk of perforation can be minimized by avoiding attempted resection of malignant lesions
7. APC following piecemeal resection can reduce recurrence rate.
8. Surveillance following resection of large polyps should take place at 3, 6 and 12 months. Biopsies of the scar should be taken. Late recurrence is a possibility. Negative scar biopsies and normal macroscopic appearance at surveillance is a good predictor of success but does not obviate the need for ongoing surveillance.
9. Endoscopic management of large polyps is unsuccessful and surgery necessary in 4-16% of cases due to recurrence, incomplete resection or presence of malignancy in the resected specimen.
10. Endoscopic management is associated with a complication rate of bleeding in 1.5-11% and perforation in 0-3%. The majority of complications are managed conservatively. Death directly related to EMR is very rare.
11. Laparoscopic surgical management is associated with complications such as infection or bleeding in 9.5-20.8%. Mortality from laparoscopic colorectal surgery is very rare.

Chapter 3- Detection of Neoplasia in the NHS Bowel Cancer Screening Programme

Chapter 3.1- Colonoscopy quality measures in the NHS Bowel Cancer Screening Programme

3.1.1 Introduction

Screening for colorectal cancer (CRC) is undertaken in many countries worldwide. One widely used strategy is biennial faecal occult blood testing (FOBT) followed by colonoscopy for those with a positive FOB test (Benson et al 2008). The main aim of CRC screening is to reduce mortality by early detection and treatment of cancer. A secondary aim is to detect and remove adenomas in order to prevent progression to cancer. Adenoma detection is known to vary widely both between and within screening programmes (Bretagne et al 2010; Atkin et al 2004; Mandel et al 2000; Kronberg et al 1996; UK Colorectal Cancer Screening Group 2004). Much of this variation may be explained by factors relating to quality of the colonoscopy. The importance of ensuring high quality colonoscopy within screening programmes has been emphasised in a number of recent studies and guidelines (Kaminski et al 2010; Rex et al 2002; Segnan et al 2011).

Adenoma detection rate (ADR) is a widely used indicator of colonoscopy quality (Millan et al 2008; it is a marker both of the technical quality of the procedure and of the efficacy of the screening strategy. Other domains of quality assessment including safety and patient experience are also crucial. A UK audit of colonoscopy published by Bowles et al 2004 raised concerns regarding the quality of colonoscopy in the United Kingdom, showing caecal intubation in only 76.9% of 9223 procedures and an overall perforation rate of 1:769. Measures have been introduced in the UK over the last decade to improve the quality of colonoscopy. These include a national endoscopy training programme, defined parameters for endoscopy training coordinated by the Joint Advisory Group on Gastrointestinal Endoscopy (JAG) and national endoscopy standards (defined by the Global Rating Score (GRS). Clear standards and accreditation of colonoscopists for bowel cancer screening were developed.

In this study, quality indicators are used to examine the quality of colonoscopy delivered within the NHS Bowel Cancer Screening programme.

3.1.2 Methods

Screening Programme

The NHS Bowel Cancer Screening Programme (BCSP) commenced in England in August 2006. During the study period, adults aged between 60 and 69 years were offered faecal occult blood testing (FOBT) on a biennial basis using a non-rehydrated guaiac-based test. Adults over 70 years were able to opt-in to the programme on a voluntary basis. The upper age limit for invited screening was extended to 74 years in January 2010. Individuals with positive FOB testing were offered colonoscopy.

Prior to commencing practice in the BCSP, all colonoscopists are required to have performed at least 1 000 colonoscopies in their career with a caecal intubation rate (CIR) above 90% and an ADR above 20% in the preceding twelve months. In addition, sedation levels have to be in keeping with National Patient Safety Agency (NPSA) recommendations and British Society of Gastroenterology (BSG) guidelines and complication rate has to be reported and deemed acceptable (National Patient Safety Agency 2004; Bell et al 1991). Completion of an accreditation examination at an independent unit is undertaken; this consists of a multiple choice question exam and performance of two colonoscopies observed by two independent and trained examiners using objective directly observed colonoscopic procedural skills (DOPs) assessment criteria (available at: <http://www.thejag.org.uk/TrainingforEndoscopists/DOPForms.aspx>). Accredited colonoscopists are subject to ongoing audit of colonoscopic performance.

For the purposes of quality assurance within the screening programme, extent of colonoscopy, quality of bowel preparation, patient comfort, colonoscope withdrawal time and rectal retroversion are recorded at the time of colonoscopy by a dedicated screening nurse present in the endoscopy room for the entire procedure. All polyps removed in the study period were sent for histopathological examination by an accredited BCSP pathologist and laboratory.

All demographic, colonoscopic and histopathological data were recorded by the screening centre on a national database (Bowel Cancer Screening System (BCSS)). Adverse events

were recorded on the BCSS, reported to the national office of the BCSP and verified by direct contact with each screening centre.

Study Procedures

Specific searches of the national database (BCSS) were designed to provide data to calculate each quality indicator (see appendix A). Missing data, where possible, were recovered from screening centres and included in the calculation of quality indicators. Data quality in the database was generally good for the data required for this study with over 98% completeness in the majority of fields (see section on data quality in General Methods). Audits comparing BCSS data with locally held records were performed demonstrating satisfactory accuracy. Entries in the database which appeared clinically implausible, as adjudicated by panel decision, were excluded from further analysis (table 16).

Variable	Plausible range	Number of implausible values n, (% of complete dataset)
Colonoscopy withdrawal time (negative and complete to caecum)	1–60 minutes	147 (2.7%)
Midazolam dose	0.5–10 mg	132 (0.36%)
Fentanyl dose	12.5–200 mcg	26 (0.07%)
Pethidine dose	12.5–200 mg	113 (0.31%)

Table 16- Limits for considering data implausible

The prevalent round of screening was defined as the first two years following commencement of screening at each centre. Any screening colonoscopies performed after two years of commencement of screening were considered to be in the first incident round (consisting of colonoscopies not performed in the prevalent round). Approval of this work as service evaluation was obtained from a regional ethics committee.

Quality Indicators

Ten quality indicators were identified and defined for the purpose of evaluation of colonoscopy in the NHS BCSP. These indicators, their definitions and level of accountability are shown in table 17.

Quality indicator	Abbreviation	Accountability	Definition
1. Adenoma detection rate	ADR	Colonoscopist	Number of colonoscopies at which one or more histologically confirmed adenomas were found divided by the total number of colonoscopies performed in the same time period
2. Polyp detection rate	PDR	Colonoscopist	Number of colonoscopies at which one or more polyps were found (regardless of histological type) divided by the total number of colonoscopies performed (in the same time period).
3. Colonoscopy withdrawal time	CWT	Colonoscopist	Average time taken to withdraw the colonoscope from the caecal pole to the anus in complete, negative procedures
4. Unadjusted caecal intubation rate	uCIR	Colonoscopist	Proportion of all colonoscopic procedures in which the caecum, terminal ileum or anastomosis was reached (no adjustment made for poor bowel preparation or impassable strictures)
5. Rectal retroversion rate	RRR	Colonoscopist	Proportion of procedures in which the colonoscope was retroverted in the rectum
6. Polyp retrieval rate	PRR	Colonoscopist	Proportion of resected polyps which were retrieved and sent for histological analysis
7. Sedation practices	-	Colonoscopist	Mean doses of pethidine, fentanyl and midazolam when used. Patient comfort assessed during colonoscopy using the modified Gloucester score to grade patient discomfort as none, mild, moderate or severe (Chilton et al 2011)
8. Buscopan use	-	Colonoscopist	Proportion of procedures in which hyoscine n-butyl bromide (Buscopan) was administered.
9. Bowel preparation scores	-	Screening centre	Quality of bowel preparation assessed by colonoscopist at the time of colonoscopy using a 4 point modified Likert scale. Descriptors for quality of bowel preparation were: incomplete examination due to inadequate preparation; complete examination despite inadequate preparation; adequate or excellent preparation (Chilton et al 2011).
10. Adverse events	AE	Colonoscopist/ Screening centre/unit.	Data from BCSS, AE log and screening centres

Table 17- Colonoscopy quality indicators

Where quality indicators were calculated as an average per colonoscopist or screening centre, only those having performed over 50 procedures were included in analysis. A cut-off of 50 procedures was chosen as below this number the confidence intervals around a point estimate of ADR are too wide and there is insufficient statistical power. In part, the basis for this cut-off was to allow reliable comparison of a colonoscopist's ADR with the minimum standard ADR recommended by the NHS BCSP Quality Assurance Guidelines (Chilton et al 2011). This document recommends the use of 80% confidence intervals for proactive quality assurance. A colonoscopist would need to have performed a minimum of 50 procedures to allow an ADR of 25% to be statistically significantly below the 35% standard. At less than 50 procedures the confidence intervals are too wide for use in quality assurance. Table 18 illustrates the ADR and associated 80% confidence intervals depending on number of procedures performed. Values are in bold in the right-hand column if the upper confidence limit excludes 35%.

No of procedures	No with ≥ 1 adenoma	Point estimate ADR	80% confidence limits*
200	50	25%	21.0% - 29.4%
100	25	25%	19.4% - 31.4%
60	15	25%	17.7% - 33.6%
48	12	25%	16.9% - 34.7%
40	10	25%	16.2% - 35.9%
20	5	25%	12.7% - 41.5%
8	2	25%	6.9% - 53.8%
4	1	25%	2.6% - 68.0%

Table 18- with associated 80% confidence intervals (from Chilton et al 2011)

In general screening terms the ADR can be referred to as the positive predictive value (PPV) for adenoma(s), that is the proportion (%) of individuals undergoing colonoscopy with one or more adenomas. To avoid double-counting of adenomas only first screening colonoscopies were included in the analysis. Measures of neoplasia detection, other than ADR, may provide additional information for quality assessment of colonoscopy. Other measure include polyp detection rate (PDR, number of colonoscopies at which one or more polyps (regardless of

removal or histological subtype) were found divided by the total number of colonoscopies), mean adenomas per procedure (MAP, total number of adenomas detected divided by the number of procedures) and mean adenomas per positive procedure (MAP+, total number of adenomas detected divided by the number of procedures in which one or more adenoma were detected). The role of PDR, MAP and MAP+ in assessing the quality of colonoscopy is less clear than that of ADR, I therefore calculated PDR, MAP and MAP+ for each colonoscopist and compared the measures with ADR using tests of correlation.

Colonoscopy withdrawal time (CWT) was recorded (to the nearest whole minute) by a nurse at the time of colonoscopy. Only complete, negative procedures were included in analysis to remove the impact of therapeutic manoeuvres on the procedure duration. Mean negative complete withdrawal time (nc-CWT) was calculated per colonoscopist.

Caecal intubation was recorded at the time of colonoscopy and based on the colonoscopist's assessment of extent of intubation using anatomical landmarks. Unadjusted caecal intubation rate (uCIR) was calculated on an intention to reach the caecum basis: no adjustment for pathology, strictures or bowel preparation quality was made. Obtaining photographic evidence of caecal intubation is stipulated in the BCSP but was not reviewed for the purposes of this study. In order to be considered satisfactory indicators of colonoscopy quality, technical factors such as uCIR, CWT, RRR and PRR should correlate with ADR. The relationships between ADR and these factors were assessed.

Adverse events were defined as those which prevented completion of the planned procedure (excluding technical failure or poor preparation) or resulted in admission to hospital, prolongation of existing hospital stay, another interventional procedure or subsequent medical consultation (Chilton et al 2011). Adverse events were classified in terms of severity according to a stratification tool defined by the BCSP Quality Assurance Guidelines for Colonoscopy (figure 10) (Chilton et al 2011). This tool is based on a report from the ASGE workshop on colonoscopy related adverse events (Cotton et al 2010). In order to capture all adverse events, patients were encouraged to contact their local screening centre if any problems arose following discharge. In addition, a questionnaire, which specifically requested information on any adverse events experienced, was sent to all patients 30 days following their procedure. Records of colonoscopy related adverse events were obtained from two sources (interrogation of the BCSS database and analysis of the log of adverse events

reported to the national office). These were validated against locally held records of adverse events at each screening centre which were examined in a national survey of adverse events.

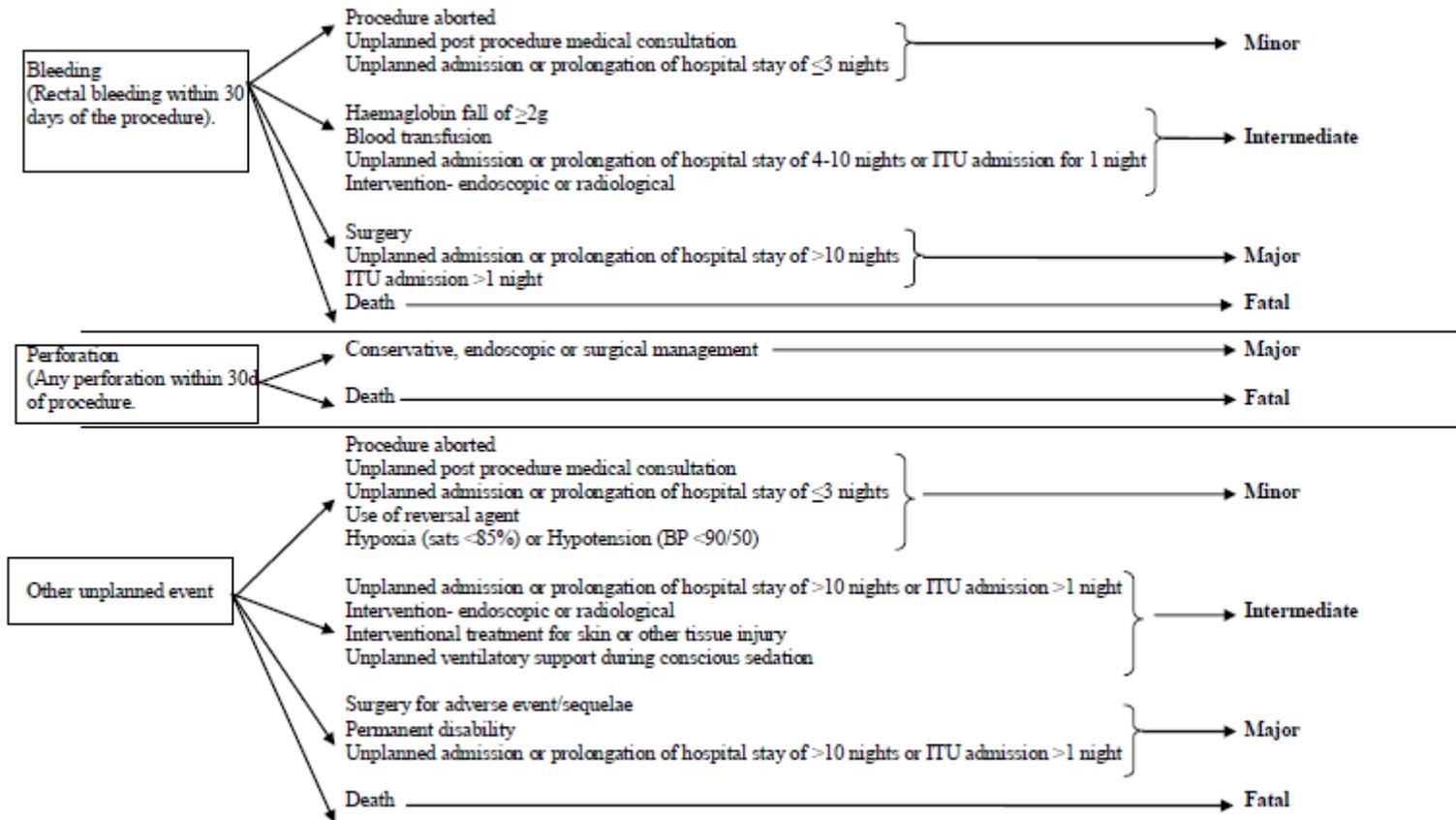


Figure 10- Stratification of complications arising from colonoscopy in the NHS Bowel Cancer Screening Programme

Statistical analysis

Normally distributed continuous variables were presented as mean (range). Categorical variables were presented as a proportion (%). Where categorical variables are summarized for the whole sample, a mean proportion (%) as well as a range of individual proportions are presented (e.g. mean adenoma detection rate (ADR) for all colonoscopists (%), lowest ADR per colonoscopist– highest ADR per colonoscopist). Univariable analysis was undertaken using a two sample T-test to compare continuous variables and the χ^2 test for categorical variables. Correlation of normally distributed continuous variables was assessed using Pearson's correlation coefficient (r). Correlation of non-parametric variables was assessed with the Spearman Rank correlation coefficient (ρ). A p value of less than 0.05 was considered to be statistically significant. All reported p values are two sided. All analyses were performed with Stata (version 10, Statacorp, Texas, USA).

A summary flowchart of the study methodology is shown in figure 11. A flowchart of the numbers of patients included in the study at each stage of the data collection process is shown in figure 12.

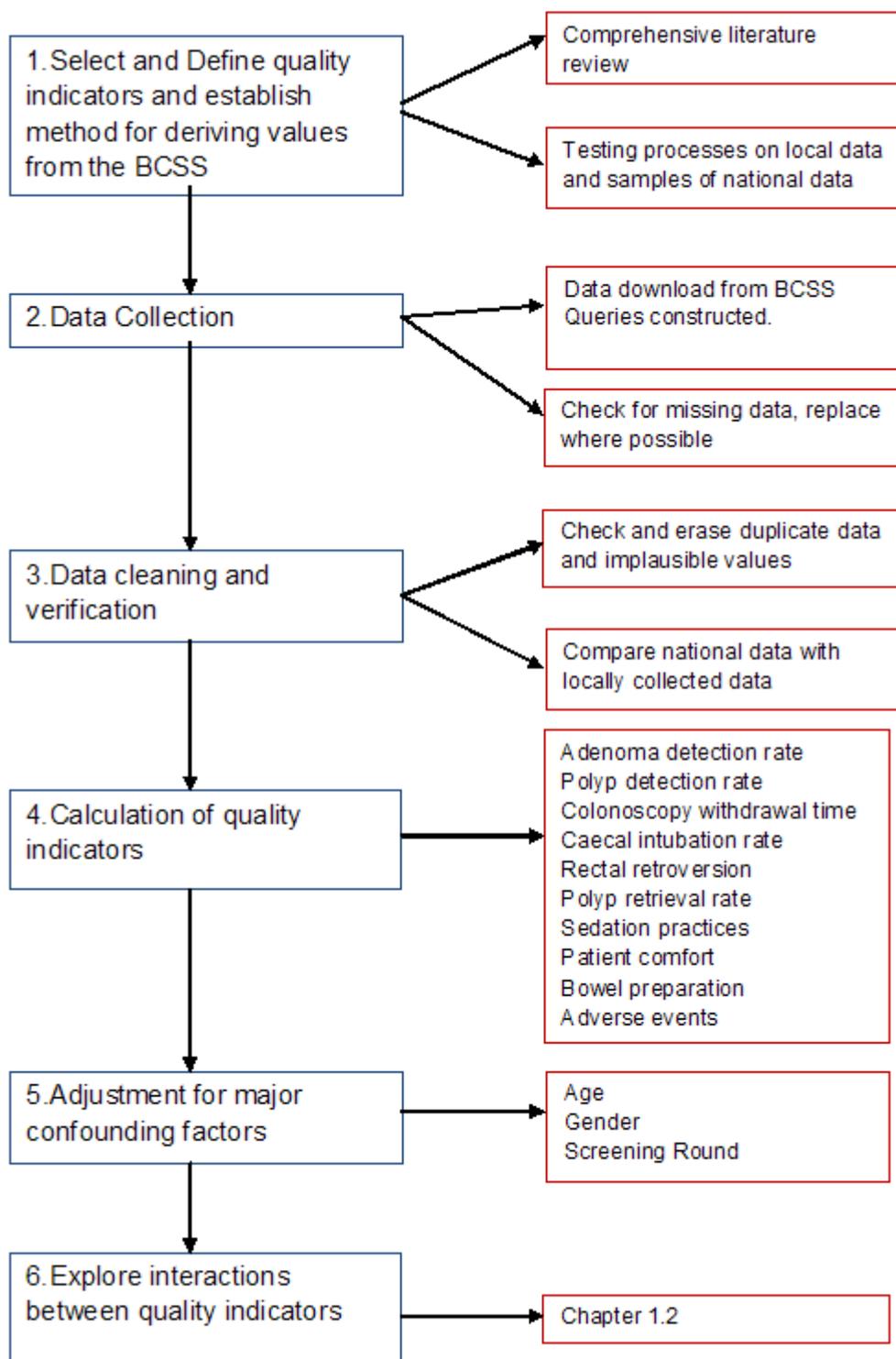


Figure 11- Flowchart of methodology for chapter 2.1.1

Flowchart of the data collection process

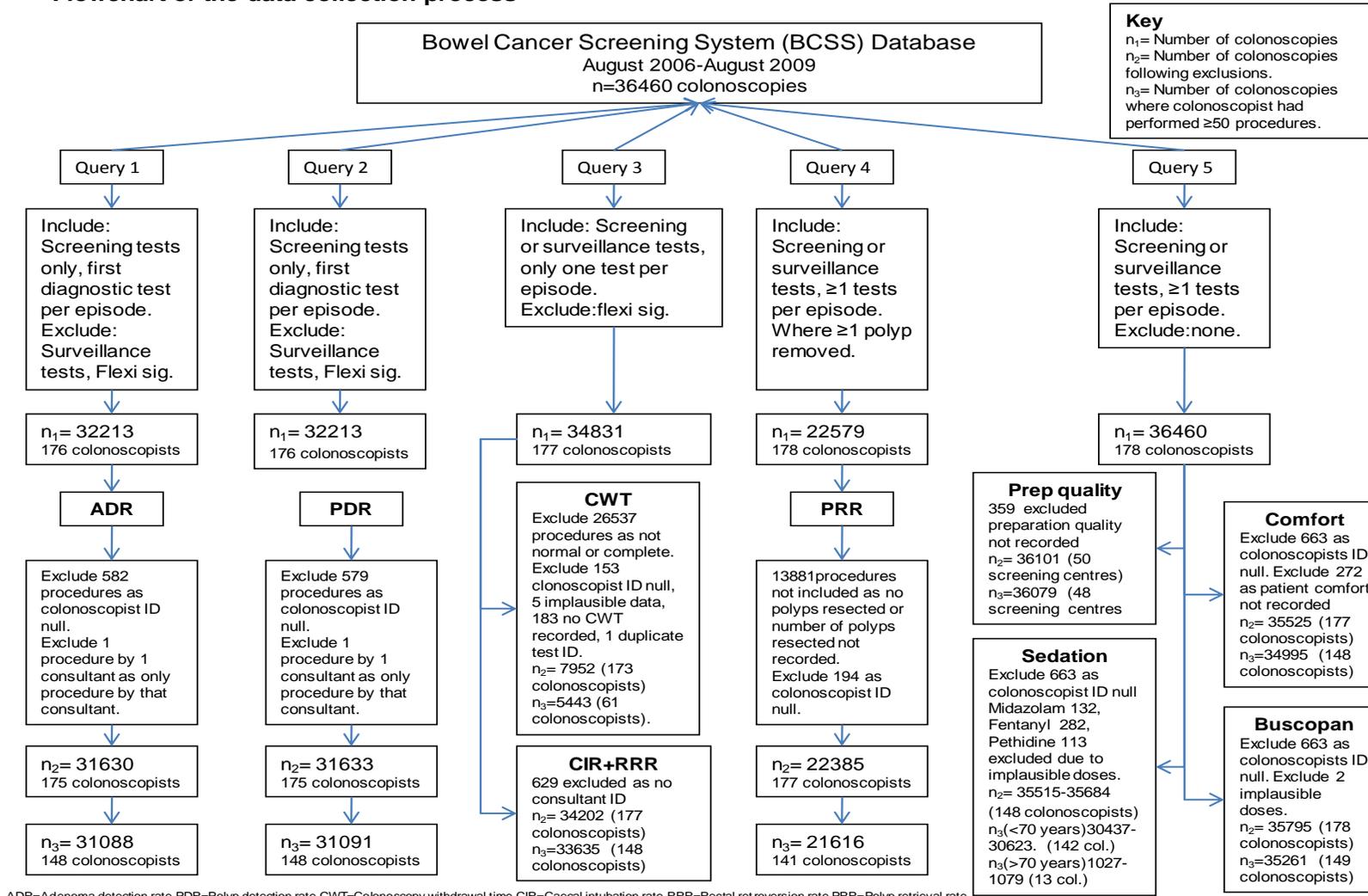


Figure 12- Flowchart of the data collection process

3.1.3 Results

Colonoscopy Quality Indicators

Between August 2006 and August 2009, 2 269 983 individuals completed FOB testing. Uptake of FOB testing was 52.9%. 2.02% of FOB tests positive. 36 460 colonoscopies and 1708 sigmoidoscopies were performed by 177 different colonoscopists at 50 screening centres. The mean age of patients undergoing colonoscopy was 66.0 years (range 60–92 years). 61.6% were male. 3848 cancers were detected at colonoscopy with a positive predictive value of colonoscopy (following positive FOB testing) for cancer of 10.6%.

Summary data for each of the quality indicators attributable to the colonoscopist are shown in table 19. The denominator is different for each indicator due to differing definitions of eligible procedures and differences in missing or implausible data between each variable.

	Mean per colonoscopist	Range	Denominator (number of procedures counted)
Adenoma detection rate	46.5%	21.9–59.8 %	31 088 by 148 colonoscopists
Polyp detection rate	59.7%	39.8–76.3 %	31 091 by 148 colonoscopists
Mean colonoscopy withdrawal time	9.4 minutes	5.6–12.3 minutes	5 443 by 61 colonoscopists
Unadjusted caecal intubation rate	95.2%	76.2–100 %	33 635 by 148 colonoscopists
Rectal retroversion rate	89.5%	27.0–100 %	33 635 by 148 colonoscopists
Polyp retrieval rate	92.7%	68.9–100 %	21 616 by 141 colonoscopists

Table 19- Summary data for colonoscopist attributable quality indicators

Adenoma detection rate

ADR per colonoscopist ranged from 21.9% to 59.8% with a mean of 46.5% (median 47.2%). ADR is a key metric for measuring quality of colonoscopy and may be used to compare two or more colonoscopists, it is therefore important to consider major confounding factors such as gender, age and screening round. It is known that adenomas are more common in males and incidence increases with age (Rex et al 1995, Johnson et al 1990). In our study, the mean ADR per colonoscopist in males was 52.9% and the mean ADR in females 36.5% ($p < 0.001$). ADR was therefore standardised by gender (GS-ADR) to allow for variation in the proportion of males and females in the case-mix of a particular colonoscopist. For the majority of colonoscopists these two measures (ADR and GS-ADR) were closely matched (mean difference between ADR and GS-ADR was -0.02, sd 0.93). Older patients in the screening population undergoing colonoscopy were more likely to have one or more adenomas. The ADR in patients less than 65 years of age was 44.0% compared to 48.2% in those age 65 or older ($p < 0.001$). However, there was little variation in the average age of patients undergoing colonoscopy between colonoscopists (mean age 65.8 years, SD= 0.6, range 64.2-67.9). The mean difference between the ADR and the age-standardised (AS-ADR) for all colonoscopists was 0.13 (sd 1.73). In addition, ADR and GS-ADR correlate strongly ($r = 0.99$, $p < 0.001$), as do ADR and AS-ADR ($r = 0.96$, $p < 0.001$), the crude ADR was therefore an adequate measure for the data presented here.

Analysis of ADR in colonoscopies occurring in the prevalent round (P-ADR) and in the first incident round (I1-ADR) was performed. The prevalent round was defined as the first two years following commencement of screening at an individual centre, during this period all individuals in the target age range would be offered FOB screening once. The first incident round was defined as the next 2 year period; the majority of individuals would be receiving their second invitation to FOB screening, a minority would be receiving their first if they had entered the target age range. The P-ADR in 28 607 prevalent round colonoscopies was 46.2% compared to 46.3% in 2 882 incident round colonoscopies ($p = 0.90$). Therefore, no standardization of ADR by screening round was required.

ADR per colonoscopist correlates positively with caecal intubation rate ($\rho = 0.203$, $p = 0.013$), mean nc-CWT ($\rho = 0.236$, $p = 0.004$) (figure 13), rectal retroversion rate ($\rho = 0.193$, $p = 0.019$) and polyp retrieval rate ($\rho = 0.241$, $p = 0.003$). No correlation between ADR and bowel

preparation quality (per colonoscopist, $p=0.086$, $p=0.300$) or comfort score ($p= -0.004$, $p=0.958$) is seen; both these measures were subjectively assessed.

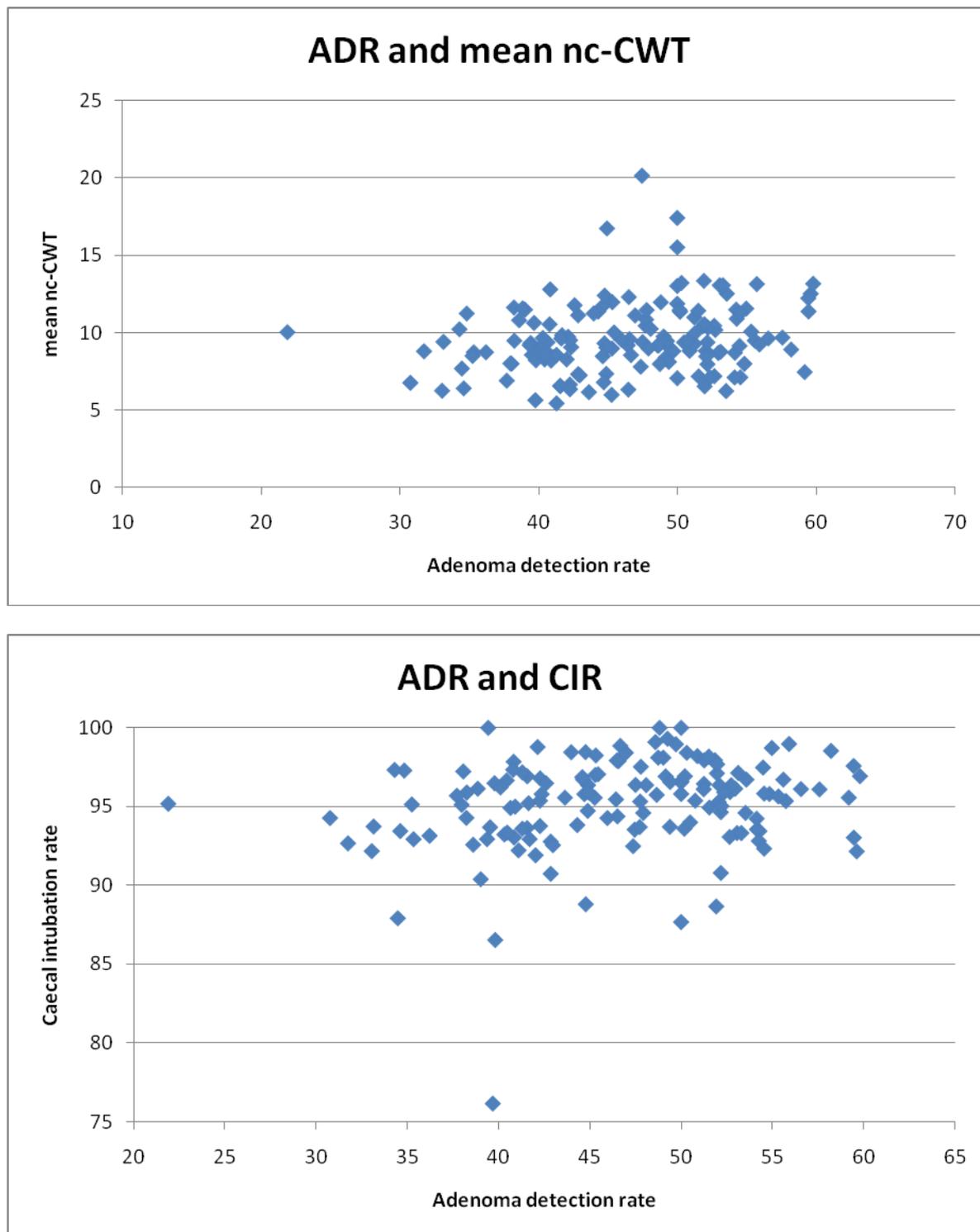


Figure 13- Scatterplots of colonoscopy withdrawal time and caecal intubation rate against adenoma detection rate per colonoscopist. MAP (mean adenomas per procedure) and ADR were shown to be positively correlated (table 20), this is largely because 53.0% of individuals

with one or more adenomas have only one adenoma. MAP+ correlates less well with ADR as it is possible for a colonoscopist to have a MAP+ near or above the mean with a low ADR.

The relationship between ADR, MAP and MAP+ are demonstrated in figure 14.

Correlating MAP with caecal intubation rate ($\rho=0.21$, $p=0.009$), mean nc-CWT ($\rho=0.30$, $p<0.001$), rectal retroversion rate ($\rho=0.17$, $p=0.03$) and polyp retrieval rate ($\rho=0.25$, $p=0.002$) produces very similar relationships as ADR with these measures. This is because ADR and MAP are so closely correlated. MAP+ is not amenable to correlation with these measures in view of the unreliability of MAP+ when it is low.

	Mean	Range	Standard deviation	Correlation with ADR (r)
ADR	46.5%	21.9-59.8%	7%	n/a
MAP	0.91	0.31-1.86	0.25	0.85 ($p<0.001$)
MAP+	1.94	1.3-3.1	0.35	0.54 ($p<0.001$)

Table 20- Others measures of neoplasia detection at colonoscopy and their relationship with ADR

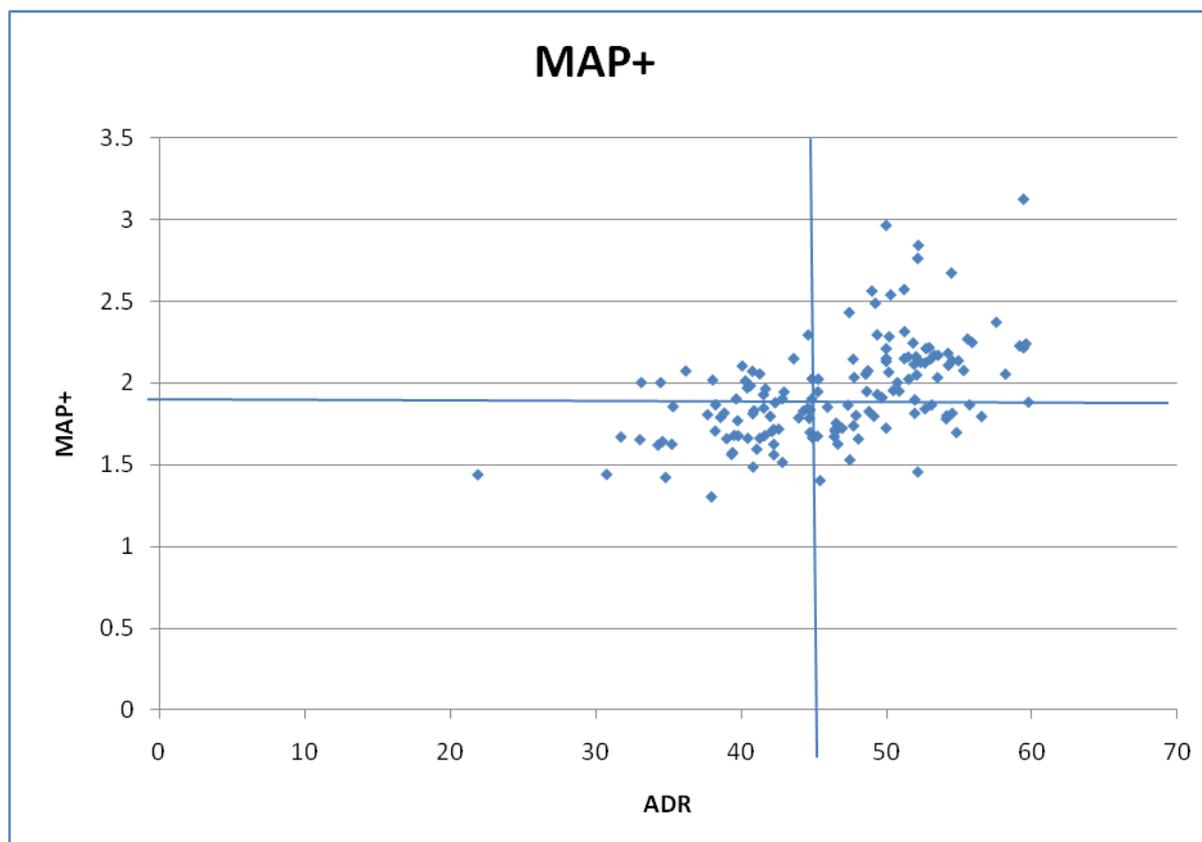
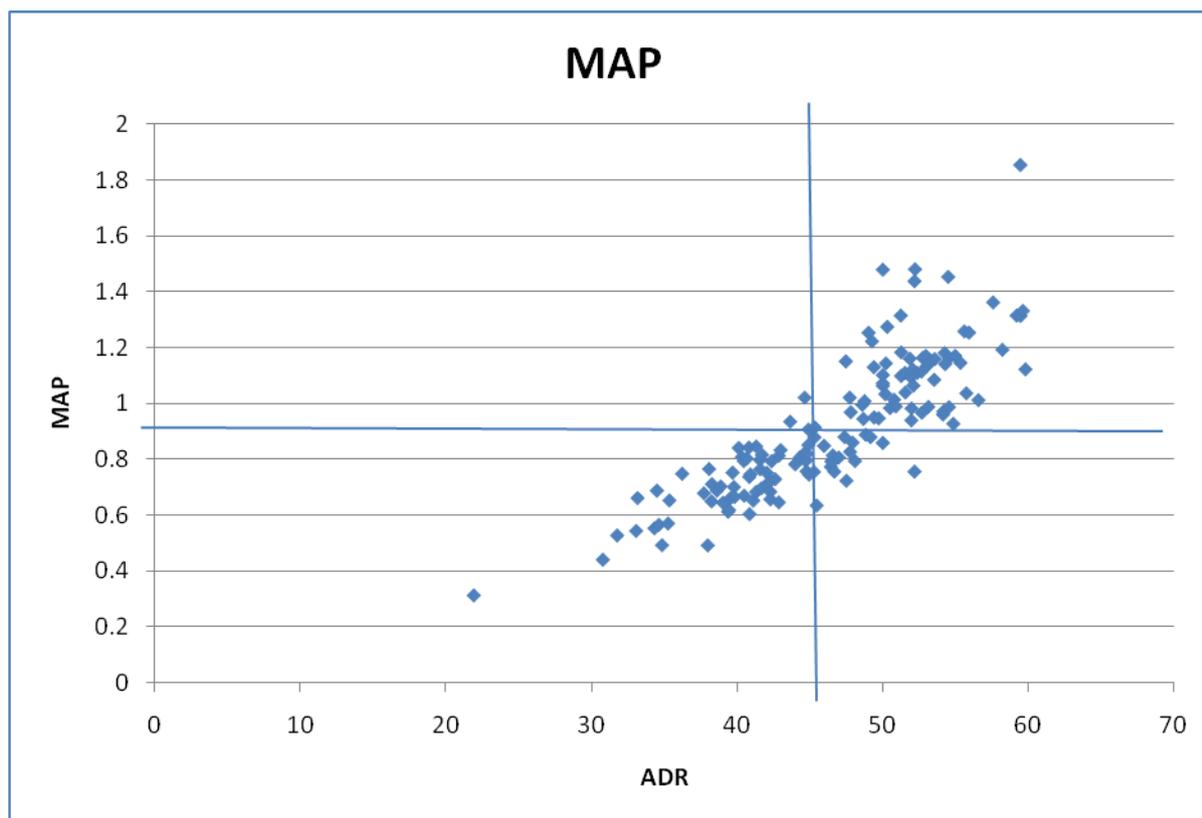


Figure 14-Scatterplots of MAP and MAP+ against ADR per colonoscopist. Blue lines in the chart represent the respective means of the measures for the population.

Sedation Practice, antispasmodic use, patient comfort and bowel preparation quality

Mean doses of the most frequently used benzodiazepine and opiate medications are shown in table 21 sub-grouped into under 70 years and 70 and over age groups. The mean percentage per colonoscopist of patients receiving no sedation was 14.1% (range 0–63.0%).

	Mean dose (range of means per colonoscopist)	
Mean midazolam dose	<70 years	2.23mg (1.0–4.4)
	≥70 years	2.13mg (1.0–4.5)
Mean fentanyl dose	<70 years	59.3mcg (25–100)
	≥70 years	60.1mcg (29.5–100)
Mean pethidine dose	<70 years	33.5mg (22.6–50)
	≥70 years	30.7mg (19.0–53.2)

Table 21- Mean sedative doses

Among colonoscopists who performed unsedated colonoscopy less frequently than the mean, 89.0% of procedures were associated with no, minimal or mild discomfort. This figure was 89.6% for colonoscopists who performed unsedated colonoscopy more frequently (p=0.62). Mean adenoma detection rates were the same in both groups (46.5%, p=0.97).

Entonox (nitrous oxide and air, BOC, UK) was used at least once, either alone or in combination with other medications, by 32 of 149 (21.5%) colonoscopists who had performed 50 or more procedures. Among these colonoscopists, 10.0% of procedures were performed with Entonox but no intravenous sedation (range 0.1-47.5%). Propofol was used at least once by 14/149 colonoscopists accounting for 0.75% of procedures (range 0.1-2%). The use of reversal agent was infrequent with flumazenil or naloxone used in 0.15% and 0.66% of procedures respectively.

Hyoscine n-butyl bromide (Buscopan), used as an intravenous antispasmodic to aid visualization of the colonic mucosa, was used in more than 80% of procedures by 31 of 149 colonoscopists (20.8%). The mean proportion of procedures per colonoscopist in which buscopan was used was 32.7% (range 0–98.1%).

Nurse assessed patient comfort scores during colonoscopy were as follows: 64.3% (range 23.9-100%) of patients had no or minimal discomfort during colonoscopy; 24.9% (0–59.5%) reported mild discomfort; 9.6% (0–31.1%) reported moderate discomfort and 1.3% (0–10.4%) reported severe discomfort. The mean proportion of procedures in which the bowel preparation was excellent or adequate was 94.2% (range 81.5–100%).

Adverse events

All centres completed a detailed record of all adverse events. Table 22 shows the incidence of complications in the NHS BCSP. Adverse events were stratified according to their severity. 49 major or intermediate severity bleeds occurred (0.13%), this excludes minor bleeds not requiring transfusion, intervention or prolonged admission (less than 3 nights). 35 perforations occurred (0.09%). Ten other adverse events requiring admission for three or more nights or surgical intervention occurred (0.03%). These included two episodes of obstruction secondary to cancer, two splenic injuries requiring surgery, one stroke, two adverse reactions to bowel preparation and three prolonged admissions due to pain. No deaths occurred as a result of screening colonoscopy.

		Number	Incidence (%, n=38 168)
Bleeding	Minor	106	0.28
	Intermediate	45	0.12
	Major	4	0.01
	Fatal	0	0
Perforation			
	Major	35	0.09
	Fatal	0	0
Other unplanned event			
	Minor	75	0.20
	Intermediate	6	0.02
	Major	4	0.01
	Fatal	0	0

Table 22- Incidence of adverse events, classified according the BCSP QA guidelines stratification tool

3.1.4 Discussion

This study demonstrates high quality colonoscopy in the NHS Bowel Cancer Screening Programme. These data show that colonoscopy in a national screening programme can be delivered to a high standard whilst ensuring patient comfort and safety. These standards are achieved despite the BCSP being one of the largest colorectal cancer screening programmes in the world (Benson et al 2008).

The most widely used metric for assessing colonoscopy quality is the adenoma detection rate. Our study demonstrated a mean ADR of 46.5%. This figure reflects the above average risk of detecting adenomas in FOBt positive individuals in the target age group. The ADR reported here is higher than in the pilot study of bowel cancer screening in the UK (37.1%, $p < 0.001$) (Weller et al 2007). This difference may be explained by a number of factors including the age range of the screened population and progress in technical aspects of colonoscopy such as bowel preparation quality, improved equipment and advances in colonoscopic technique. The mean CWT for normal procedures and unadjusted CIR in our study are further evidence of the high technical quality of BCSP colonoscopy and compare favourably to other reports

from large screening programmes (Regula et al 2006). These data demonstrate an improvement in the quality of UK colonoscopy when compared to the 2004 national audit in which the unadjusted CIR was 76.9% (Bowles et al 2004). This improvement in colonoscopy quality in England supports the measures employed by the Joint Advisory Group on gastrointestinal endoscopy (JAG) and the BCSP in promoting and enhancing colonoscopy quality. A national audit of colonoscopy practice in England (<http://www.endoaudit.com/>) including non-screening colonoscopy is currently being undertaken, it will provide an up-to-date opportunity to compare performance indicators for screening and non-screening colonoscopy.

Despite the overall high quality of colonoscopy demonstrated by this study, there is still considerable variation in adenoma detection rate between colonoscopists. ADR per colonoscopist ranged from 21.9 to 59.8%, an almost threefold difference between the highest and lowest detecting colonoscopists. This variation persists when ADR is standardised for age and gender and is not due to sample size variation as colonoscopists with less than 50 procedures were excluded. It is of interest that this variation exists in spite of the quality standards colonoscopists must reach prior to commencing screening colonoscopy. Variation is also seen in other technical quality indicators (nc-CWT, uCIR, RRR, PRR). Significant correlations between these measures and ADR were demonstrated. Further work is being undertaken to examine the relationship between markers of colonoscopic practice and adenoma detection in individual patients. Ongoing quality assurance work within the screening programme is needed to minimise variations in colonoscopic performance.

It is not known at present which processes will be most effective in minimising these variations, or indeed if it is possible for all colonoscopists to reach optimal standards.

This study demonstrates that routine reporting of age, gender or screening round standardised ADR is not necessary, however these methods remain useful for quality assurance purposes to investigate the effect of these variables if an individual colonoscopist is noted to have particularly low or high ADR. For instance, a colonoscopist who has colonoscoped a larger proportion of females than the mean may have a lower non-standardised ADR.

The role of MAP and MAP+ in addition to ADR for assessing technical aspects of colonoscopy quality have been explored. ADR has an inherent limitation in that it does not measure the total number of adenomas detected. MAP and MAP+ are more aligned with the ethos of colonoscopy in the BCSP which, in addition to detecting cancer, is to detect and

remove all adenomas. MAP and MAP+ may provide additional information about the performance of colonoscopists. The mean MAP for the population suggests the majority of colonoscopies result in zero, one or two adenomas being found. The scatterplot of MAP against ADR in Figure 14 identifies a group of colonoscopists who have an ADR around the mean but with a broad range of MAP. This demonstrates that some colonoscopists are able to find more adenomas per patient than others; due either to underlying variation in adenoma prevalence or due to operator based technical (or non-technical) skills of the colonoscopists themselves. MAP+ is not useful if the ADR is low, however it provides extra information where ADR is high. The group of colonoscopists with a MAP+ over 2.5 and an ADR over 50.0% appear to be capable not only of detecting adenomas in high numbers of patients but also of detecting multiple adenomas in these patients. I recommend that the BCSP routinely reports MAP and MAP+ in addition to ADR to give screening colonoscopists additional insight into their performance.

The adverse event rates in this study compare favourably with other published series which report post colonoscopy bleeding in 0.03–0.22% of procedures and perforation in 0.01%–0.8% of procedures (Weller et al 2007; Panteris et al 2009; Crisp et al 2009). The 2004 audit demonstrated low complication levels which have been maintained in this study. Given that 46.5 % of procedures require at least one polypectomy and many involve removal of large and multiple polyps the low levels of adverse events are notable.

No difference in adenoma detection rate was seen between the prevalent and first incident screening rounds. This pattern was also seen in the pilot study of the screening programme (Weller et al 2007). This is an important finding as it helps predict future colonoscopic workload for the screening programme and also allows ADR to be used as a comparative quality indicator for colonoscopists who perform different proportions of prevalent and incident round procedures.

Cancer detection rate, however, is known to be lower in subsequent incident rounds compared to the prevalent round (Weller et al 2007). The fact that relatively small numbers of cancers are detected means that whilst cancer detection rate is crucially important, it is not a sensitive measure of colonoscopy quality and tends to be dependent more on the underlying prevalence of colorectal cancer than technical skills attributable to the colonoscopist. For this reason I have not reported cancer detection rate per colonoscopist in this study.

No correlation between ADR and bowel preparation quality (per colonoscopist) was observed. Although this appears counter-intuitive, the analysis is at a per colonoscopist summary level, not at an individual procedure level. This reflects therefore, that poor bowel preparation occurred at a similar rate for all colonoscopists and, to some extent, obviates the possibility that low adenoma rate per colonoscopist could be explained by a higher proportion of poor bowel preparations. The guaiac-based FOBt screening protocol used by the BCSP is designed to achieve a yield for adenomas and advanced adenomas above that of the general population. This limits comparison of colonoscopy performance indicators reported in this study with other screening programmes employing alternative screening modalities such as faecal immunochemical testing (FIT) or flexible sigmoidoscopy, which may have differing sensitivity and specificity for neoplasia detection.

Any single quality indicator reported in this study would be insufficient in isolation to appraise the quality of colonoscopy. It is necessary to analyse a number of measures of quality as summarised in the model in figure 15. The data presented in this study provide evidence to support the use of this model to assess quality of colonoscopy.

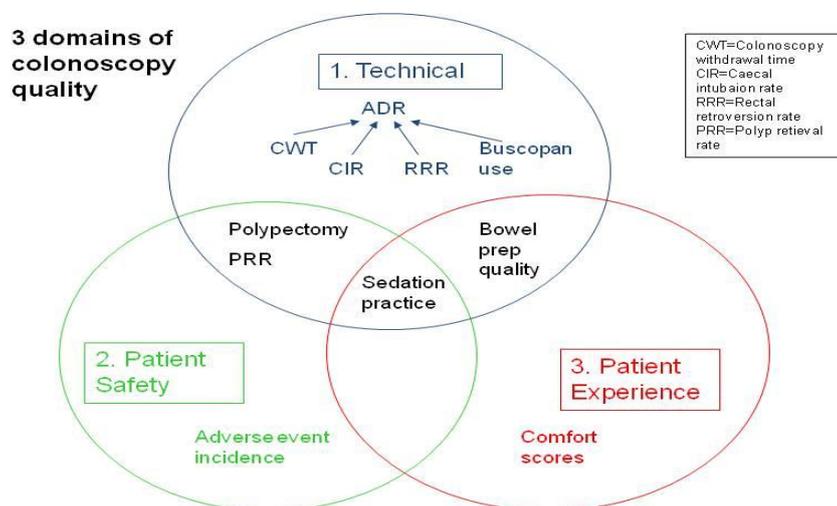


Figure 15- Three domains of colonoscopy quality assessment

An important strength of this study is its size, both in terms of the number of colonoscopies analysed and the nation-wide coverage of the programme. Many colonoscopy quality studies are either single centre or restricted to a small number of colonoscopists. These data

demonstrate that a high level of colonoscopy quality can be achieved in a large programme. Nevertheless our study has several limitations. Firstly, data for all colonoscopies were not complete, however, complete datasets accounted for 98% of all data and missing data did not cluster geographically or around individual colonoscopists. This level of missing data should have only a minor effect on the measured quality indicators. The quality of collected data is in itself a marker of quality of a screening programme and feedback on data quality issues raised by this study will improve the future quality of the data collection process (Ellis et al 2006).

Secondly, a number of the indicators relied on subjective assessments (patient comfort, bowel preparation quality) using non-validated scoring systems. This was necessitated by the absence of widely used, validated scoring systems for these measures. Common guidance on use of the scoring systems used for bowel preparation and patient comfort was given to all screening practitioners to standardise data collection. Incorporation of validated scoring systems for these measures into the BCSP colonoscopy quality assurance process is necessary.

Thirdly, clinical outcome measures, such as interval cancers, were not measured. This study concentrated on measures of colonoscopy quality which can be recorded at or close to the time of colonoscopy. Further work is being undertaken to assess the incidence of interval lesions in the NHS BCSP.

To ensure ongoing high quality colonoscopy in the BCSP, quality assurance guidelines have defined a number of auditable outcomes and quality standards.¹⁵ Auditable outcomes are defined as important indicators but as yet no clear standard exists (for example, the standard for perforation rate per colonoscopist is less than one per thousand colonoscopies). Quality standards are defined as an auditable outcome for which there is an evidence base that can support a minimum standard (table 23). These are designed to drive quality to higher standards whilst setting limits to identify suboptimal performance. The results presented here demonstrate that colonoscopic quality in the BCSP has exceeded these standards.

The incorporation of measures of total adenoma detection as targets in the quality assurance guidelines would emphasise the importance of these measures of quality. Based on the 90th percentile of each measure, a MAP of 1.20 and a MAP+ of 2.27 (providing the ADR is satisfactory) as targets are suggested.

In summary, this large national study demonstrates high quality colonoscopy in the NHS Bowel Cancer Screening Programme. The adverse event rate is low despite the need for therapy associated with high adenoma detection rates. Assessment of a range of quality indicators including measures of total adenoma detection is necessary to evaluate colonoscopy quality. Potential screening programme participants should be reassured that screening colonoscopy within the NHS Bowel Cancer Screening Programme is high quality, safe and well-tolerated.

Measure	Minimum standard	Target
Adenoma detection rate	≥35%	≥40%
Unadjusted caecal intubation rate	≥90%	≥97%
Mean colonoscopy withdrawal time (negative-complete)	≥6 minutes	≥10 minutes
Bowel prep quality (described as excellent or adequate)	≥90%	≥95%
Polyp retrieval rate	≥90%	≥95%
Perforation rate	<1 per 1000	-
Post polypectomy bleeding rate	<1 per 100	-
Comfort scores	100% recorded	-

Table 23- Minimum standards and targets for colonoscopy in the BCSP (Chilton et al 2011)

Chapter 3.2- Colonoscopy withdrawal time and adenoma detection rate in the NHS Bowel Cancer Screening Programme

3.2.1- Introduction

Increasing CWT has been shown to correlate with increasing adenoma detection rate (Rex 2000). In a study by Barclay et al (2006) of 2053 screening colonoscopies by 12 colonoscopists, those with a mean CWT of more than 6 minutes detected more than twice as many adenomas as those with mean CWT less than 6 minutes. Current US guidelines (Rex et al 2002) recommend an average CWT in normal colonoscopies of at least 6-10 minutes. Guidelines for colonoscopists in the NHS BCSP recommend a mean CWT of at least 6 minutes (Chilton et al 2011). The aim of this study was to identify the optimal mean CWT within the context of the NHS Bowel Cancer Screening Programme.

Recent studies have suggested a possible lack of protection by colonoscopy against right sided CRC (Baxter et al 2009, Brenner et al 2010). It known that increased adenoma detection is associated with reduced interval cancer risk (Kaminski et al 2010). A further aim of this study, therefore, was to examine the effect of duration of withdrawal time on right sided adenoma detection.

3.2.2- Methods

Study Population

The study population consisted of all colonoscopies performed in the NHS BCSP between August 2006 and August 2009. The indication for all colonoscopies was a positive faecal occult blood test result. Surveillance procedures (where the indication was a history adenomas) and repeat procedures were not included. The process for establishing the study population (n=31088 colonoscopies) is the result of query 1 to the National Bowel Cancer Screening Programme database as shown in figure 12 and appendix A.

Colonoscopy withdrawal time was defined as the time taken to withdraw the colonoscope from the caecal pole to the anus. CWT was measured at the time of endoscopy by a screening nurse present in the endoscopy room whose role was to record procedural data independently from the colonoscopist and endoscopy nurse. Only complete procedures in which no pathology requiring excision or biopsy was encountered were included in the calculation of

the mean negative complete colonoscopy withdrawal time (nc-CWT) in order to remove the potential bias of therapeutic manoeuvres on the duration of withdrawal. The number of adenomas detected was based on histologically confirmed adenomas only. The size of adenomas was obtained from both the colonoscopist's assessment and the pathology report with the larger measurement being used in the analyses. The site of adenomas was recorded by the colonoscopist at the time of polypectomy. Lesions at or proximal to the splenic flexure were termed right sided lesions, those distal to the splenic flexure left sided. Advanced adenomas were defined as 1cm or larger in size or displaying high grade dysplasia. Bowel preparation quality was recorded by the colonoscopist at the time of colonoscopy on a 4 point modified Likert scale (Chilton et al 2011). Descriptors were: Incomplete examination due to inadequate preparation; complete examination despite inadequate preparation; adequate or excellent. These data are recorded prospectively on the NHS BCSP national database for the purpose of quality assurance. Prospectively recorded data required for this study were retrieved from this database for analysis.

Statistical analysis

The mean negative complete colonoscopy withdrawal time (nc-CWT) and adenoma detection rates were calculated for each colonoscopist who had performed 50 or more procedures.

Colonoscopists were grouped according to their mean nc-CWT into four groups (A- <7 minutes, B- 7 to 8.9 minutes, C- 9 to 10.9 minutes, and D- ≥ 11 minutes). The four groups were chosen to have 2 minute intervals in the centre groups, to represent the distribution of mean withdrawal time among the colonoscopists and reflect existing clinical guidelines for withdrawal time (Rex et al 2002; Chilton et al 2011). The lowest group was <7 minutes (rather than <6 minutes which could have been used) to give adequate numbers of procedures in the lowest group for statistical analysis. The percentage of all procedures where one or more adenomas were detected (ADR, %) and the total number of adenomas detected per procedure were calculated. These are presented as proportions with relative risk compared to the lowest withdrawal time group. A two sample test of proportions and a test of trend were used to compare adenoma detection in each of the groups.

Multivariable analysis using logistic regression was performed to account for potential confounding factors including age, gender, smoking status, alcohol use, and bowel

preparation quality. Odds ratios with 95% confidence intervals (CI) were calculated. Analysis of advanced adenoma detection, right sided adenoma detection, and adenoma size in relation to nc-CWT was also performed. All p values are two sided, a p value of less than 0.05 was considered significant. All analyses were performed using Stata (version 10, Statacorp, Texas USA).

3.2.3- Results

31088 colonoscopies by 147 colonoscopists were analysed (mean number of procedures per colonoscopist- 211, range 51-730). The mean withdrawal time per colonoscopist in negative complete procedures (nc-CWT) varied from 5.4 to 20.1 minutes (mean 9.6 minutes). Table 24 shows the number of colonoscopists and procedures in each of the four nc-CWT groups and the characteristics of the patients in each group.

	Colonoscopy withdrawal time groups			
	A	B	C	D
	<7 minutes	7-8.9 minutes	9-10.9 minutes	>11 minutes
Number of colonoscopists	15	43	51	38
Mean nc-CWT	6.3	8.1	9.8	12.6
Median nc-CWT	6.3	8.4	9.7	11.8
Number of patients	3297	8731	12180	6880
Mean age	65.7	65.7	65.7	65.6
Male (%)	59.4	61.0	60.4	59.8
Current or ex-smokers (%)*	43.3	46.3	44.2	45.0
Alcohol use (%)*	63.6	63.8	68.3	66.5
Proportion of procedures with adequate or excellent bowel preparation quality (%)*	95.1	95.5	95.0	93.3

Table 24- Characteristics of patients in the 4 groups of colonoscopists by mean negative complete colonoscopy withdrawal time

*** Smoking status not recorded for 188 patients (0.6%), alcohol use not recorded for 304 patients (1.0%), bowel preparation quality not recorded for 248 patients (0.8%)**

Table 25 shows the adenoma detection rate and total adenoma detection rates in each group of colonoscopists. 28386 adenomas were detected in 31088 procedures (0.91 per colonoscopy). One or more adenomas were detected in 14394 procedures (46.3%). A test of trend for ADR by withdrawal group was highly significant ($p < 0.001$). There was an 11% increase in the number of procedures yielding one or more adenomas ($p < 0.001$) and a 25% increase in the total number of adenomas detected in favour of those colonoscopists with

longer withdrawal times ($p < 0.001$). Figure 16 shows the ADR in each of the withdrawal time groups.

Group	Number of procedures by colonoscopists in each group	Procedures where adenoma(s) found (ADR %) [RR][#]	Total no. of adenomas detected	Total adenomas detected per procedure [RR]	Mean number of adenomas detected in procedures where adenoma found
A	3297	1403 (42.5) [1.00]	2523	0.77 [1.00]	1.80
B	8731	3966 (45.4) [1.07]	7597	0.87 [1.14]	1.92
C	12180	5774 (47.4) [1.11]	11776	0.96 [1.26]	2.04
D	6880	3252 (47.3)* [1.11]	6490	0.94 [1.23]	2.00
Total	31088	14394 (46.3)	28386	0.91	1.97

Table 25- Adenoma detection rate and total adenomas detection rates for each withdrawal time group (univariable analysis)

[#] Relative risk

* Test of trend for ADR by group $p < 0.001$

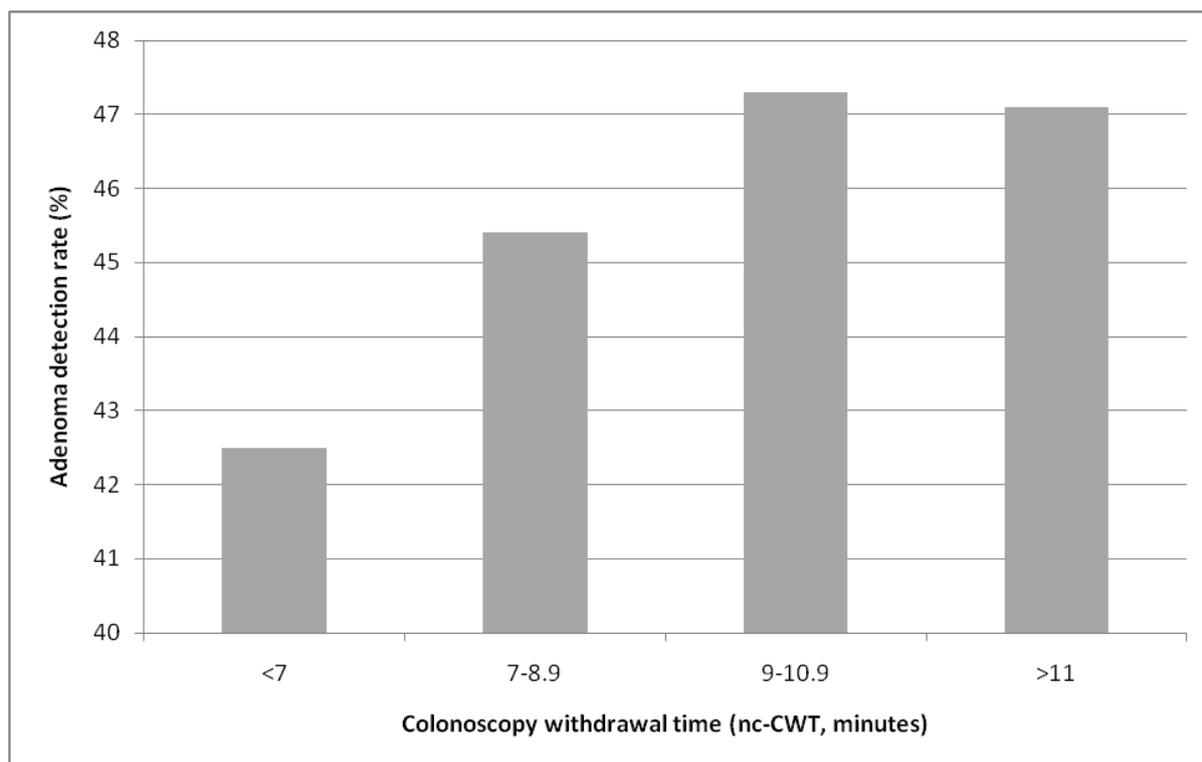


Figure 16- Graph of ADR (%) per colonoscopist against mean nc-CWT (minutes) by group (univariable analysis)

Site and size of adenoma and advanced adenomas

Colonoscopists with longer withdrawal times detected around 50% more right sided adenomas per procedure than those with shorter withdrawal times (Group D- 0.35 right sided adenomas per procedure, Group A- 0.23 right sided adenomas per procedure, $p < 0.001$).

Longer withdrawal times were also associated with an increase in left sided adenoma detection but with only a 10% difference between the longest and shortest withdrawal time groups (Group D- 0.59 left sided adenomas per procedure, Group A- 0.54 left sided adenomas per procedure, $p < 0.001$).

Group D colonoscopists detected 50% more small adenomas than Group A colonoscopists. No increase in detection of larger adenomas (≥ 1 cm) was seen with longer withdrawal times. Similarly, no increase in advanced adenoma detection was seen in the longer withdrawal time groups (Table 26).

Group	Total number of adenomas detected*	Percentage of adenomas on right side (%)	Number of left side adenomas detected per procedure (RR)	Number of right sided adenomas detected per procedure (RR)	Percentage of adenomas less 1cm (%)	Number of adenomas \geq 1cm in size detected per procedure (RR)	Number of adenomas < 1cm in size detected per procedure (RR)	Number of procedures where \geq1 advanced adenoma(s) detected (%)	Relative risk of detecting \geq1 advanced adenoma
A	2523	30.1	0.54 (1.00)	0.23 (1.00)	54.1	0.351 (1.00)	0.414 (1.00)	950 (28.8)	1.00
B	7597	33.2	0.58 (1.09)	0.29 (1.26)	58.5	0.361 (1.03)	0.509 (1.23)	2576 (29.5)	1.02
C	11776	36.5	0.61 (1.14)	0.35 (1.53)	62.9	0.358 (1.02)	0.606 (1.46)	3508 (28.8)	1.00
D	6490	37.3 [#]	0.59 (1.10)	0.35 (1.53)	65.0 [†]	0.329 (0.94)	0.611 (1.48)	1954 (28.4) [∞]	0.99
Total	28386								

Table 26- Withdrawal time related to site and size of adenoma detection and advanced adenoma detection

* includes all adenomas detected – some procedures detecting more than one adenoma

[#] Test of trend for percentage of right sided adenomas by group $p < 0.001$

[†] Test of trend for percentage of adenomas less than 1cm by group $p < 0.001$

[∞] Test of trend for proportion of procedures with ≥ 1 advanced adenoma $p > 0.05$

Potential confounding factors

Age, gender, smoking, and alcohol use are factors that may affect the probability of finding an adenoma in an individual (Lieberman et al 2000; Anderson et al 2003; Martinez et al 1995). These potential confounding factors are similar between groups (table 24) and therefore not likely to have any major influence on the conclusions of the univariable analysis. Logistic regression models with and without these potential confounding factors are shown in table 27 showing that adjusting for these factors has minimal impact on the relationship between withdrawal time and adenoma detection rate. Figure 17 shows the adjusted odds ratio for detecting adenomas with increasing withdrawal time.

Group	No allowance	Allowing for age, sex, drinking and smoking	Allowing for age, sex, drinking, smoking and bowel preparation*
A	1.00	1.00	1.00
B	1.12 (1.04-1.22)	1.11 (1.02-1.20)	1.10 (1.01-1.19)
C	1.21 (1.12-1.31)	1.19 (1.10-1.29)	1.19 (1.10-1.29)
D	1.20 (1.11-1.31)	1.18 (1.09-1.29)	1.21 (1.11-1.32)

Table 27- Odds ratio (95% CI) for detection of adenoma before and after allowing for confounding factors using logistic regression

*** Bowel preparation quality (percentage described as excellent or adequate)**

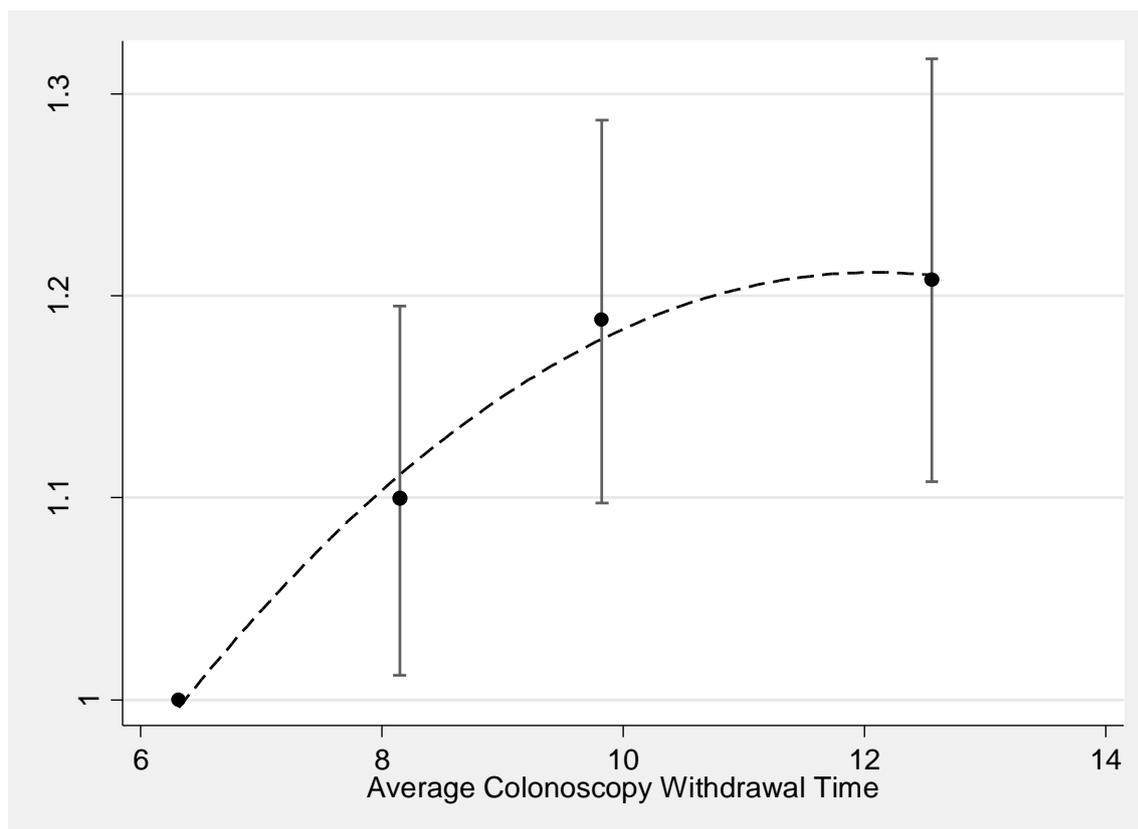


Figure 17- Graph of odds ratio (with 95% CI) for detecting adenoma versus nc-CWT, after allowing for confounding factors (age, sex, drinking, smoking and bowel preparation)

3.2.4- Discussion

This is the largest study to demonstrate an association between CWT and ADR, and the first study in a screening population that had undergone FOB testing. This study demonstrates that, even within a high quality screening programme, adenoma detection rate increases with longer mean negative colonoscopy withdrawal time. Previous studies have suggested a minimum CWT of 6 to 8 minutes (Rex et al 2002; Barclay et al 2008; Simmons et al 2006); our study demonstrates an optimum mean nc-CWT of 10 minutes. Above an nc-CWT of 10 minutes, further increase in mean withdrawal time does not significantly increase ADR. This is evidence of the ‘ceiling effect’ (Tabar et al 2010; Vicari et al 2010), which may be explained by the presence of a finite number of detectable adenomas within a colon.

An important strength of this study is its size. This is in comparison to previous studies of withdrawal time which are often single centre studies or restricted to a handful of colonoscopists. The number of colonoscopists covered by this study allows variation in

colonoscopic performance to be demonstrated despite the requirement that all colonoscopists have previously demonstrated high levels of colonoscopic competence prior to commencing screening colonoscopy.

Our study reinforces the findings of Simmons et al (2006) that increasing ADR with increasing withdrawal time is due to detection of more small adenomas. Contrary to the findings of Barclay et al (2006), no increase in advanced adenoma detection with increasing withdrawal time was seen in our study. This may be because the withdrawal time ceiling for detecting advanced adenomas is lower and is already achieved by the baseline mean withdrawal time in our population of colonoscopists (no colonoscopist had a mean withdrawal time lower than 5.4 minutes). The ethos of colonoscopy in the Bowel Cancer Screening Programme however, is to detect and remove all adenomas. This strategy has underpinned the success of randomised controlled trials and pilot studies of FOB screening for colorectal cancer (Scholefield et al 2002; Kronborg et al 2004; UK Colorectal Cancer Screening Group 2004). In addition, the detection rate of all adenomas rather than advanced adenomas, is recommended as a better quality indicator of screening colonoscopy (Rex et al 2002). The increase in detection of smaller lesions is important therefore, both clinically and as a performance indicator.

A recent Canadian community based study concluded that screening colonoscopy did not confer any protection from right sided CRC (Baxter et al 2009). In our study, longer withdrawal times resulted in detection of more right sided adenomas. A recent German study (Brenner et al 2011) has suggested that high quality screening colonoscopy may be more protective against right sided cancer than the Canadian study suggested. The authors attribute this, in part, to major efforts in terms of training and quality assurance. Proximal colorectal neoplasia may be harder to detect or have a different natural history to distal lesions with earlier malignant transformation (Singh et al 2006; Nawa et al 2008; Arain et al 2010). Our study demonstrates the importance of withdrawal time in detecting right sided lesions. Longer withdrawal time, as a marker of colonoscopic quality, may have contributed to the reduction in risk for both right and left sided CRC seen in the German study.

Our study has a number of limitations. Firstly, we have not examined the relationship between CWT and a longer term clinical outcome measure such as interval cancer rate. A recent study has shown no detectable association between withdrawal time and risk of future neoplasia following screening colonoscopy (Gellad et al 2010). However, baseline

withdrawal time was calculated from only 304 procedures where no polyps were detected. The mean withdrawal time at baseline (calculated per medical centre) was 12 minutes. This may be indirect evidence of the ‘ceiling effect’ we describe here and suggests that CWT is a more relevant measure of colonoscopic performance below 10 minutes. A Polish study has shown a negative correlation between increasing ADR and risk of interval cancer (Kaminski et al 2010). This study did not include data on withdrawal times. Prospective analysis of colonoscopy quality indicators with interval neoplasia rate in the NHS BCSP is being undertaken.

Secondly, although this study lacks the advantages of a prospective randomised controlled trial, the data were collected prospectively by an independent screening practitioner for the purpose of quality assurance. Due to the availability of data regarding a range of potential confounding factors, we have been able to control for these in the analysis. A number of known risk factors for colorectal adenomas, such as family history or nonsteroidal anti-inflammatory drug (NSAID) use were not available for inclusion in the multivariable analysis. Individuals with known familial risk factors for colorectal cancer under surveillance were not included in the screening programme. NSAID use was unlikely to differ between the groups or change the conclusions of this study.

Thirdly, the choice of groupings could be criticised on the basis that there were fewer colonoscopists in the shortest withdrawal time group. The data were re-analysed with five groups with more equal numbers of colonoscopists in each group (results not shown), the results were similar. The conclusions that the optimal mean withdrawal time was around 10 minutes, lower withdrawal times were too short to optimise adenoma detection and mean withdrawal times of 11 minutes or more did not improve ADR, were confirmed.

Fourthly, the study population was restricted to FOB positive screening programme participants in the screening programme target age range. Therefore, the external validity of these findings outside the context of screening colonoscopy is not clear. It is known that increasing CWT is associated with increasing ADR in non-screening populations (Barclay et al 2006; Simmons et al 2006, however, the clinical objective of non-screening colonoscopy may not be to detect and remove all neoplasia. The trade off between increasing procedure duration and detection of more adenomas is not clear-cut outside screening colonoscopy. The common indication for all the colonoscopies in our study however, minimises any bias that

could be introduced by variation in indication for colonoscopy between colonoscopists had the study been conducted in a non screening setting.

Finally, we have assumed that screening colonoscopists utilise the withdrawal phase of colonoscopy to perform detailed mucosal inspection for neoplasia. Some lesions may be detected during the insertion phase and some colonoscopists may perform a longer, more detailed examination on insertion requiring less time on withdrawal. The use of mean nc-CWT should account for this variation in practice across the population of colonoscopists. Studies of the effect on ADR of the introduction of a minimum CWT have had mixed results. Barclay et al (2008) set a minimum CWT of 8 minutes in conjunction with advice on optimal withdrawal technique leading to an increase in ADR from 23.5% to 34.7%. Sawhney et al (2008) however, did not find an increase in polyp detection rate (PDR) when they studied the effect of the introduction of a policy of a minimum CWT of seven minutes in one institution.

We cannot make any firm conclusions from this study about whether it is the duration of withdrawal that is accounting for the change in ADR or simply that longer nc-CWT is a marker of good colonoscopic technique. It may be that manoeuvres to improve mucosal inspection (which incidentally increases CWT) such as re-positioning the patient, adequate insufflation and suction, meticulous mucosal re-inspection, retro-fold examination, and rectal retroversion are performed more frequently by 'good' colonoscopists leading to higher ADR and longer mean nc-CWT. We recommend that screening colonoscopists 'actively' inspect the colonic mucosa using these manoeuvres rather than passively withdrawing the colonoscope. A study of an intervention to increase the nc-CWT in BCSP screening colonoscopists with an nc-CWT below 10 minutes, with ADR as the outcome variable, would be of value.

In summary, the findings of this study demonstrate an optimal mean nc-CWT per colonoscopist for screening colonoscopy of 10 minutes. Increasing adenoma detection associated with longer withdrawal times is dependent on increasing detection of right sided and sub-centimetre adenomas. These findings reinforce the value of CWT as a metric of colonoscopy quality.

Chapter 3.3- Patient and colonoscopy factors affecting adenoma detection in patients undergoing colonoscopy in the NHS Bowel Cancer Screening Programme

3.3.1- Introduction

Screening for CRC with biennial faecal occult blood testing (FOBT) and colonoscopy for those with a positive FOBT has been demonstrated to reduce mortality from CRC by 15 to 18% (Hewitson et al 2007). Reduction in mortality is mainly achieved through detection of cancer at an earlier stage.

A secondary, objective of colonoscopy in an FOBT screening programme is detection and removal of all adenomas. Removal of adenomas, particularly large (10mm or greater in size) or histologically advanced (displaying high grade dysplasia) adenomas may prevent progression to cancer. In the National Polyp Study, removal of adenomas at colonoscopy was associated with a 76 to 90% risk reduction of CRC in people with colorectal polyps (Winawer et al 1993).

Adenoma detection is also important from a quality assurance perspective. Adenoma detection rate (ADR) is widely regarded as the key performance indicator of colonoscopy (Rex 2005). Increasing ADR has been shown to correlate with decreased interval cancer rate (Kaminski et al 2010).

Multiple factors may affect whether an adenoma is detected during colonoscopy. These include patient factors which influence whether or not the patient has an adenoma. These may be non-modifiable (male gender, family history and increasing age are all associated with increased adenoma incidence) (Lynch et al 2003; Lieberman et al 2003) or modifiable (cigarette smoking and alcohol use are associated with increased adenoma incidence) (Anderson et al 2003; Reid et al 2003; Anderson et al 2005; Martinez et al 1995).

Additionally, there are colonoscopy related factors which determine whether an adenoma is detected. These factors, such as caecal intubation, colonoscopy withdrawal time or bowel preparation quality, relate to the completeness of pan colonic mucosal inspection for adenomas and are important as they are potentially modifiable, offering the opportunity to optimise adenoma detection (Harewood et al 2003; Barclay et al 2006; Chen et al 2007).

Few previous studies have included the full range of currently known, measurable technical variables of colonoscopy in addition to modifiable and non-modifiable patient factors to examine the risk of an adenoma being detected. This approach is necessary to allow for confounding between potential risk factors and enables known risk factors for neoplasia to be controlled for whilst examining the role of potentially modifiable aspects of colonoscopy practice which are associated with an increased risk of adenoma detection.

The aim of this study was to identify patient factors and colonoscopy technical factors associated with increased or decreased risk of adenoma detection in patients in the NHS BCSP.

3.3.2- Methods

Study Population

All colonoscopies in the NHS Bowel Cancer Screening Programme (BCSP) between August 2006 (when the screening programme commenced) and August 2009 were analysed. The indication for all procedures was a positive FOB test. Surveillance colonoscopies were not included and where an individual had more than one procedure in a screening episode, only the first procedure was included in order to avoid double-counting of adenomas.

Demographic and lifestyle data (date of birth, gender, smoking status, alcohol consumption, height (metres), weight (kg), postal code) were collected from individuals prior to colonoscopy during a pre-colonoscopy assessment with a trained screening practitioner. These data are recorded on the BCSS database to which colonoscopy data are added at the time of the procedure. Histological data for any lesions detected at colonoscopy are also recorded on the database.

Data were obtained from the BCSS database in April 2010. During the study period 36,460 lower gastrointestinal endoscopic procedures were performed. 32,213 of these were index colonoscopies in a screening episode. 583 procedures were excluded where the colonoscopist was not recorded. Only procedures performed by colonoscopists who had performed 50 or more procedures were included in subsequent analysis because with fewer procedures, statistical analysis per colonoscopist is underpowered. 31,088 procedures were therefore eligible for inclusion in further analysis. The process for establishing the study population

(n=31,088 colonoscopies) is the result of query 1 to the National Bowel Cancer Screening Programme database as shown in figure 12 and appendix A.

Study Procedures

Data downloaded from the BCSS database were cleaned and checked. Where possible, missing data were retrieved from the Screening Centre. Completeness of data was validated by cross checking with local data sources. Data entries for continuous variables (height, weight, drug doses and withdrawal time) which were considered implausible, as adjudicated by panel decision, were excluded from further analysis.

Age was recorded on the date of colonoscopy rather than at entry to the screening programme. Age was analysed both as a continuous variable and as a categorical variable (<62.5, 62.5-64.9, 65.0-67.49, ≥ 67.5 years). Univariable analysis showed the effect of age was more easily interpreted as a categorical variable. Smoking status was categorised as current smoker, ex-smoker or never smoked. Alcohol use was categorised as either current use or not. Patient body mass index (BMI, kg/m^2) was calculated from self-reported height and weight measurements and grouped into two categories (<25.0 and ≥ 25.0 kg/m^2). Deprivation scores were assigned using an individual's postcode at the time of entry to the screening programme. Postal codes were linked to Index of Multiple Deprivation scores (IMD) at the Lower Super Output Area level (Department of Communities and Local Government. Indices of Deprivation 2007). In subsequent analysis the IMD scores of the study population were ranked in quintiles from highest to lowest deprivation scores where group 1 was the most deprived and group 5 the least deprived.

The BCSP is coordinated by 5 Hubs which cover England. Hubs are responsible for inviting individuals to join the screening programme and conducting FOB testing. The Hub in which the individual lived at the time of invitation to the screening programme was included in the study as a geographical variable.

Colonoscopy data recorded at the time of the procedure included caecal intubation (as evidenced by anatomical landmarks), withdrawal time (defined as the time taken to withdraw the colonoscope from the caecal pole to the anus), rectal retroversion, sedative medication or intravenous antispasmodic (hyoscine n-butyl bromide) use and quality of bowel preparation. Bowel preparation quality was recorded on a four point Likert scale. Descriptors for bowel

preparation quality were: incomplete examination due to inadequate preparation; complete examination despite inadequate preparation; adequate or excellent preparation (Chilton et al 2011).

Mean colonoscopy withdrawal times were calculated for each colonoscopist for negative complete procedures only (nc-CWT). Use of actual withdrawal times for individual procedures is not appropriate as it is influenced by the duration of therapeutic procedures rather than time spent examining the colonic mucosa during withdrawal. Mean nc-CWT per colonoscopist were further categorised into two groups (<10 minutes, ≥10 minutes) based on exploratory analyses suggesting that colonoscopists with mean nc-CWT ≥10 minutes tended to have higher ADR than those with shorter mean withdrawal times. Each colonoscopy was therefore categorized based on the mean nc-CWT of the colonoscopist performing the procedure.

Univariable analysis suggested a relationship between procedure start time and adenoma detection. The association appeared to depend on how early in the morning or afternoon session the procedure was commenced. Procedure start time was divided into two groups. In group one, the procedure commenced towards the start of either a morning or afternoon session (8am-11am or 2-4pm); group two consisted of procedures starting later in a session (11am-2pm or 4-6pm).

All colonoscopists in the BCSP must have completed at least 1000 procedures during their career prior to obtaining accreditation to commence screening colonoscopy. To account for colonoscopist experience of screening colonoscopy, procedures were grouped into those among the first 300 procedures performed by an individual colonoscopist and subsequent procedures. The cut off at 300 procedures was determined by univariable analysis which showed no significant relationship when groups of 100 or 200 procedures were used. Finally, procedures were assigned to a group depending on whether intravenous sedative or analgesic medication was used. Entonox (nitrous oxide and air) may have been used in the group that didn't receive intravenous medications.

The results of each colonoscopy were categorised into one of five different outcomes: negative (no adenomas detected), one or more adenomas detected, one or more advanced adenomas detected (defined as adenomas 1cm or greater in size or displaying high grade dysplasia or polyp cancer), one or more right-sided adenomas (lesions at or proximal to the splenic flexure) and one or more rectal adenomas detected. Only lesions which were

histologically confirmed as adenomas were counted. The total number of adenomas counted at each colonoscopy was also recorded.

Statistical Analysis

Normally distributed continuous variables are presented as mean (standard deviation- sd). Categorical variables are presented as total proportions and percentages (n,%). Univariable analysis was performed using the χ^2 test for comparing categorical variables and the unpaired t-test for continuous variables. This exploratory testing identified variables which were associated with the presence of one or more adenomas. The procedure was repeated to identify variables associated with the presence of one or more advanced adenomas, right sided adenomas and rectal adenomas. In order to allow for confounding between variables, multivariable analysis using binary logistic regression to calculate odds ratios (OR) with 95% confidence intervals (CI) was performed. Four separate models (with ≥ 1 adenomas, ≥ 1 advanced adenomas, ≥ 1 right sided adenomas and ≥ 1 rectal adenomas as the dependent variables) were analysed using the forward logistic regression approach. The following patient variables were tested: gender, age, smoking status, alcohol use, BMI category, deprivation quintile, hub area. The following colonoscopy variables were tested: caecal intubation, rectal retroversion, colonoscopist's mean nc-CWT group, bowel preparation quality, hyoscine use, procedure start time group, colonoscopist's prior experience group and intravenous sedation group. Variables were included in the multivariable models if they reached a significance level of ≤ 0.1 in univariable testing. An ordinal logistic regression approach was used to analyse the effect of patient and colonoscopy factors on the total number of adenomas detected. The Pearson χ^2 test was used to assess goodness of fit of models. A p value of less than 0.05 was considered significant. All reported p values are two sided. Analyses were undertaken using SPSS version 17.0[®] (SPSS Inc., Chicago, Illinois, USA).

3.3.3- Results

Patient and procedure characteristics

31,088 colonoscopies were analyzed. These were performed by 148 colonoscopists. 18,761(60.3%) procedures were on male patients. The mean age of patients at colonoscopy in

males was 65.8 years (sd 3.75 years) and in females 65.7 years (sd 3.73 years, $p=0.051$). One or more adenomas were detected in 9918 of 18761 procedures in males (52.9%) and in 4505 of 12327 procedures in females (36.5%, $p<0.001$). One or more advanced adenomas were detected in 6248 (33.3%) males and in 2737 (22.2%) females ($p<0.001$). One or more right sided adenomas were detected in 4385 (23.4%) males and 1614 (13.1%) females ($p<0.001$).

Patient Factors

Demographic and lifestyle characteristics of the study population are shown in table 28 with univariable analyses for each of the outcome variables. BMI was not significantly associated with any of the adenoma outcomes so was not included in subsequent multivariable analysis.

	Patients (n=31088) number (%)	≥1 adenoma (n=14423) number (%)	p	≥1 advanced adenoma (n=5999) number (%)	p	≥1 right sided adenoma (n=8985) number (%)	p
Gender							
Female	12327 (39.7)	4505 (36.5)	<0.001	2737 (22.2)	<0.001	1614 (13.1)	<0.001
Male	18761 (60.3)	9918 (52.9)		6248 (33.3)		4385 (23.4)	
Age (years)							
<62.5	8415 (27.1)	3644 (43.3)	<0.001	2273 (27.0)	<0.001	1418 (16.9)	<0.001
62.5-64.9	4959 (16.0)	2235 (45.1)		1351 (27.2)		954 (19.2)	
65-67.49	6844 (22.0)	3181 (46.5)		2009 (29.4)		1322 (19.3)	
≥67.5	10870 (35.0)	5363 (49.3)		3352 (30.8)		2305 (21.2)	
Smoking*							
Never	17039 (54.8)	7280 (42.7%)	<0.001	4481 (26.3)	<0.001	2937 (17.2)	<0.001
Ex-smoker	10344 (33.3)	5145 (49.7%)		3323 (32.1)		2138 (20.7)	
Current smoker	3517 (11.3)	1923 (54.7%)		1136 (32.3)		891 (25.3)	
Alcohol**							
No	10422 (33.5)	4069 (39.0)	<0.001	2363 (22.7)	<0.001	1596 (15.3)	<0.001
Yes	20364 (65.5)	10233 (50.3)		6547 (32.1)		4349 (21.4)	
BMI[#] (kg/m²)							
<25.0	6588 (21.2)	3020 (45.8)	0.179	1869 (28.4)	0.226	1249 (19.0)	0.376
≥25.0	19413 (62.4)	9085 (46.8)		5660 (29.2)		3778 (19.5)	
Deprivation Group^{##}							
1 (most deprived quintile)	6215 (20.0)	2765 (44.5)	<0.001	1620 (26.1)	<0.001	1201 (19.3)	0.909
2	6216 (20.0)	2837 (45.6)		1703 (27.4)		1226 (19.7)	
3	6217 (20.0)	2876 (46.3)		1781 (28.6)		1189 (19.1)	
4	6217 (20.0)	2933 (47.2)		1888 (30.4)		1192 (19.2)	
5 (least deprived quintile)	6207 (20.0)	3005 (48.4)		1989 (32.0)		1188 (19.1)	
Hub area							
Midlands	9369 (30.1)	4191 (44.7)	<0.001	2601 (27.8)	<0.001	1726 (18.4)	<0.001
South	5633 (18.1)	2740 (48.6)		1764 (31.3)		1056 (18.7)	
London	4636 (14.9)	1966 (42.4)		1107 (23.9)		976 (21.1)	
North-East	4864 (15.6)	2375 (48.8)		1540 (31.7)		905 (18.6)	
Eastern	6586 (21.2)	3151 (47.8)		1973 (30.0)		1336 (20.3)	

* Smoking status of patient not known for 188 procedures (0.60%)

**Alcohol usage of patient not known for 302 procedures (0.97%)

#BMI of patient not known for 5807 procedures (18.7%)

##Postcode (and deprivation index) of patient not known for 16 procedures (0.05%)

Table 28- Patient characteristics and proportions of patients with one or more adenomas, advanced adenomas or right sided adenomas

	Patients (n=31088) number (%)	≥1 adenoma (n=14423) number (%)	p	≥1 advanced adenoma (n=5999) number (%)	p	≥1 right sided adenoma (n=8985) number (%)	p
Caecal Intubation							
No	1365 (4.4)	244 (17.9)	<0.001	151 (11.1)	<0.001	57 (4.2)	<0.001
Yes	29723 (95.6)	14179 (47.7)		8834 (29.7)		5942 (20.0)	
Rectal retroversion							
No	3115 (10.0)	1433 (46.0)	0.645	1001 (32.1)	<0.001	589 (18.9)	0.581
Yes	27973 (90.0)	12990 (46.4)		7984 (28.5)		5410 (19.3)	
Colonoscopist mean nc-CWT (minutes)							
<10	19816 (63.7)	9020 (45.5)	<0.001	5769 (29.1)	.280	3609 (18.2)	<0.001
≥10	11272 (36.3)	5403 (47.9)		3216 (28.5)		2390 (21.2)	
Bowel preparation quality							
Inadequate preparation	1637 (5.3)	620 (37.9)	<0.001	360 (22.0)	<0.001	277 (16.9)	0.011
Excellent or adequate	29280 (94.7)	13775 (47.0)		8610 (29.4)		5708 (19.5)	
Hyoscine use							
No	20521 (66.0)	9129 (44.5)	<0.001	5629 (27.4)	<0.001	3718 (18.1)	<0.001
Yes	10567 (34.0)	5294 (50.1)		3356 (31.8)		2281 (21.6)	
Start time of procedure							
8-10.59 am or 2-3.59pm	19635 (66.7)	9244 (47.1)	0.010	5810 (29.6)	0.003	3857 (19.6)	0.125
11am-1.59pm or 4-5.59pm	9790 (33.3)	4453 (45.5)		2732 (27.9)		1849 (18.9)	
Prior colonoscopist experience in the BCSP (number of procedures)							
0-299	27844 (89.6)	12858 (46.2)	0.027	7972 (28.6)	0.002	5290 (19.0)	<0.001
≥300	2344 (10.4)	1565 (48.2)		1013 (31.2)		709 (21.9)	
Sedation							
Used	27012 (86.9)	12422 (46.0)	<0.001	7750 (28.7)	0.036	5149 (19.1)	0.007
Not used	4076 (13.1)	2001 (49.1)		1235 (30.3)		850 (20.9)	

Table 29- Colonoscopy characteristics and proportions of patients with one or more adenomas, advanced adenomas and right sided adenomas

Multivariable analysis

Table 30 shows the multivariable models for the association between patient factors and adenoma detection, advanced adenoma detection and right sided adenoma detection. Most of the associations seen in univariable analysis persisted in the multivariable models when confounding factors were adjusted for. The Pearson χ^2 goodness of fit test gave p values of 0.077, 0.264 and 0.478 for each of the models respectively (a p value >0.05 suggests the model fits adequately).

Male gender (odds ratio (OR) for ≥ 1 adenomas 1.77 (95% confidence interval 1.68-1.86), $p < 0.001$) and caecal intubation (OR for ≥ 1 adenomas 3.71 (3.12-4.33), $p < 0.001$) had the strongest association with the detection of one or more adenomas, advanced adenomas or right sided adenomas. Increasing age group was associated with increased detection of one or more adenomas or advanced adenomas beyond 65 years of age (OR 1.32 (1.24-1.40) and 1.23 (1.15-1.31) for those in the ≥ 67.5 age compared to the youngest age range group respectively). However, the risk of one or more right sided adenomas increased in each consecutive age group from age 60 years. Current smoking (OR 1.61 (1.49-1.75), $p < 0.001$) is associated with a higher risk of one or more adenomas than non-smoking, this risk is also greater than that associated with ex-smoking (OR 1.17 (1.11-1.23), $p < 0.001$). Current alcohol use was associated with an odds ratio of 1.30 (1.24-1.37) for each of the outcome variables ($p < 0.001$) (figure 18).

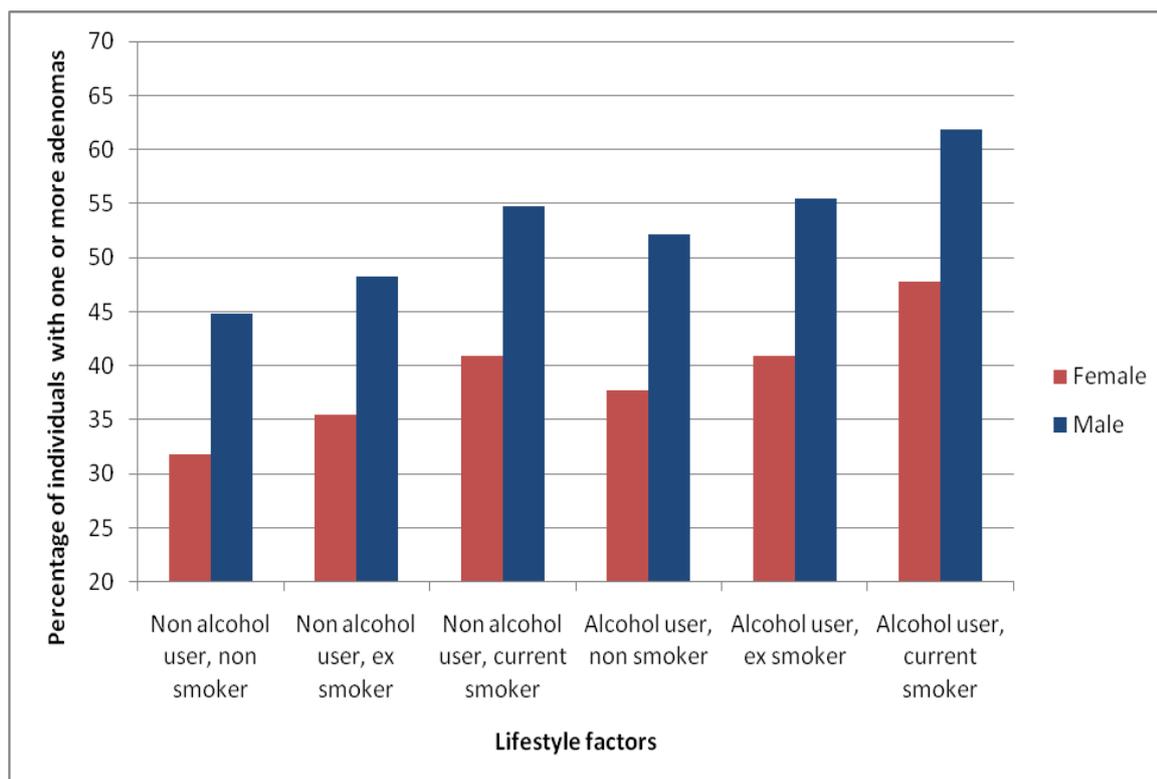


Figure 18- Impact of lifestyle factors and gender on adenoma detection in males and females

Adenoma and advanced adenoma detection was greatest in the least deprived quintile. This relationship was not seen for right sided adenomas. A geographical variation in adenoma detection is seen even when all available variables are adjusted for. In table 3 the Midlands are presented as the reference group (being the largest). The Midlands area and London have similar adenoma detection (OR 0.99 (0.92-1.07), $p=0.517$) but Southern, Eastern and North-East areas have higher adenoma detection (OR 1.21 (1.13-1.31), 1.26 (1.17-1.34) and 1.19 (1.11-1.27) respectively, all $p < 0.001$).

	Adjusted odds Ratio (95% CI) for one or more adenomas	p	Adjusted odds Ratio (95% CI) for one or more advanced adenomas	p	Adjusted odds Ratio (95% CI) for one or more right sided adenomas	p
Gender						
Female	1.00		1.00		1.00	
Male	1.77 (1.68-1.86)	<0.001	1.55 (1.46-1.64)	<0.001	1.88 (1.76-2.01)	<0.001
Age (years)						
<62.5	1.00		1.00		1.00	
62.5-64.9	1.08 (1.00-1.16)	.048	1.03 (0.94-1.11)	.559	1.20 (1.09-1.32)	<0.001
65-67.49	1.17 (1.09-1.25)	<0.001	1.15 (1.07-1.24)	<0.001	1.22 (1.12-1.33)	<0.001
≥67.5	1.32 (1.24-1.40)	<0.001	1.23 (1.15-1.31)	<0.001	1.41 (1.31-1.52)	<0.001
Smoking						
Never	1.00		1.00		1.00	
Ex-smoker	1.17 (1.11-1.23)	<0.001	1.17 (1.11-1.24)	<0.001	1.09 (1.02-1.16)	<0.001
Current smoker	1.61 (1.49-1.75)	<0.001	1.34 (1.22-1.45)	<0.001	1.57 (1.44-1.72)	<0.001
Alcohol						
No	1.00		1.00		1.00	
Yes	1.30 (1.24-1.37)	<0.001	1.38 (1.30-1.46)	<0.001	1.27 (1.18-1.35)	<0.001
Deprivation Group			-			
1 (most deprived quintile)	1.00		1.00		-	
2	1.07 (0.99-1.15)	0.102	1.09 (1.00-1.18)	0.056	-	
3	1.09 (1.01-1.17)	0.034	1.15 (1.06-1.25)	0.001	-	
4	1.10 (1.01-1.19)	0.022	1.22 (1.12-1.33)	<0.001	-	
5 (least deprived quintile)	1.15 (1.06-1.24)	0.001	1.32 (1.21-1.44)	<0.001	-	
Hub area						
Midlands	1.00		1.00		1.00	
South	1.21 (1.13-1.31)	<0.001	1.25 (1.15-1.35)	<0.001	1.12 (1.03-1.23)	0.012
London	0.99 (0.92-1.07)	0.517	0.91 (0.83-0.99)	0.026	1.43 (1.30-1.57)	<0.001
North-East	1.26 (1.17-1.34)	<0.001	1.35 (1.25-1.47)	<0.001	1.17 (1.06-1.28)	0.002
Eastern	1.19 (1.11-1.27)	<0.001	1.17 (1.08-1.26)	<0.001	1.26 (1.16-1.37)	<0.001

Table 30- Patient factors- multivariable analysis for one or more adenomas, advanced adenomas or right sided adenomas (colonoscopy factors in the same models shown in table 31)

Colonoscopy Factors

Table 29 shows colonoscopy factors and univariable associations with each outcome variable. Caecal intubation was achieved in 95.6% of procedures and was significantly associated with increased detection of one or more adenomas, advanced adenomas and right sided adenomas (all $p < 0.001$). Rather than exclude incomplete procedures from multivariable analysis, this variable was included in the logistic regression to adjust for caecal intubation. Rectal retroversion did not affect the detection of adenomas or right sided adenomas ($p=0.645$ and 0.581 respectively), and was performed in fewer patients with one or more advanced adenomas (28.5% vs 32.1%, $p < 0.001$). Further analysis was performed to examine the effect of rectal retroversion on rectal adenoma detection. In 27973 procedures where rectal retroversion was performed, one or more rectal adenomas were detected in 2523 procedures (9.0%), compared to 3115 procedures in which rectal retroversion was not performed where one or more rectal adenomas were detected in 273 procedures (8.8%, $p=0.666$). The relationship between rectal retroversion and rectal adenoma detection did not change when age and gender were accounted for.

Procedures performed by a colonoscopist whose mean nc-CWT was ≥ 10 minutes were more likely to detect one or more adenomas or right sided adenomas ($p < 0.001$) than those with a mean nc-CWT less than 10 minutes. No difference was seen between the two nc-CWT groups in advanced adenoma or rectal adenoma detection ($p=0.280$ and 0.935 respectively).

Multivariable Analysis

The colonoscopy variables (mean nc-CWT ≥ 10 minutes, excellent or adequate bowel preparation, intravenous antispasmodic use and colonoscopists prior experience >300 procedures) are all associated with an increase in adenoma detection with statistically significant odds ratios between 1.10 (1.05-1.16) and 1.38 (1.23-1.54) (table 31).

Procedures starting later in a session (11am-2pm or 4-6pm) were associated with a reduction in detection of adenomas and advanced adenomas (OR 0.94 (0.90-0.99), $p=0.018$ and 0.93 (0.88-0.98) $p < 0.001$) compared to procedures starting between 8am and 11am or 2pm and 4pm (figure 19).

In univariable analysis, procedures in which no intravenous sedation was used were associated with lower adenoma, advanced adenoma and right sided adenoma detection

however, once other variables were adjusted for in the multivariable models, no significant difference in outcome was seen between the two groups.

	Adjusted odds Ratio (95% CI) for one or more adenomas	p	Adjusted odds Ratio (95% CI) for one or more advanced adenomas	p	Adjusted odds Ratio (95% CI) for one or more right sided adenomas	p
Caecal Intubation						
No	1.00	<0.001	1.00	<0.001	1.00	<0.001
Yes	3.71 (3.12-4.33)		3.34 (2.77-4.02)		5.55 (4.17-7.4)	
Rectal retroversion						
No	-		1.00	<0.001	-	
Yes	-		0.64 (0.59-0.70)		-	
Mean nc-CWT (minutes)						
<10	1.00	<0.001	-		1.00	<0.001
≥10	1.10 (1.05-1.16)		-		1.28 (1.20-1.36)	
Bowel preparation quality						
Inadequate preparation	1.00	<0.001	1.00	<0.001	1.00	0.035
Excellent or adequate	1.38 (1.23-1.54)		1.39 (1.22-1.57)		1.16 (1.01-1.33)	
Hyoscine use						
No	1.00	<0.001	1.00	<0.001	1.00	<0.001
Yes	1.29 (1.23-1.36)		1.29 (1.22-1.36)		1.22 (1.15-1.30)	
Start time of procedure						
8-10.59 am or 2-3.59pm	1.00	0.018	1.00	<0.001	-	
11am-1.59pm or 4-5.59pm	0.94 (0.90-0.99)		0.93 (0.88-0.98)		-	
Prior colonoscopist experience in the BCSP (number of procedures)						
0-299	1.00	<0.001	1.00	<0.001	1.00	<0.001
≥300	1.20 (1.11-1.30)		1.23 (1.13-1.24)		1.38 (1.22-1.47)	
IV Sedation						
Used	1.00	0.143	1.00	0.210	1.00	0.866
Not used	1.06 (0.98-1.14)		1.05 (0.97-1.14)		1.01 (0.93-1.10)	

Table 31- Colonoscopy factors- multivariable analysis for one or more adenomas, advanced adenomas or right sided adenomas (patient factors in the same models shown in table 30)

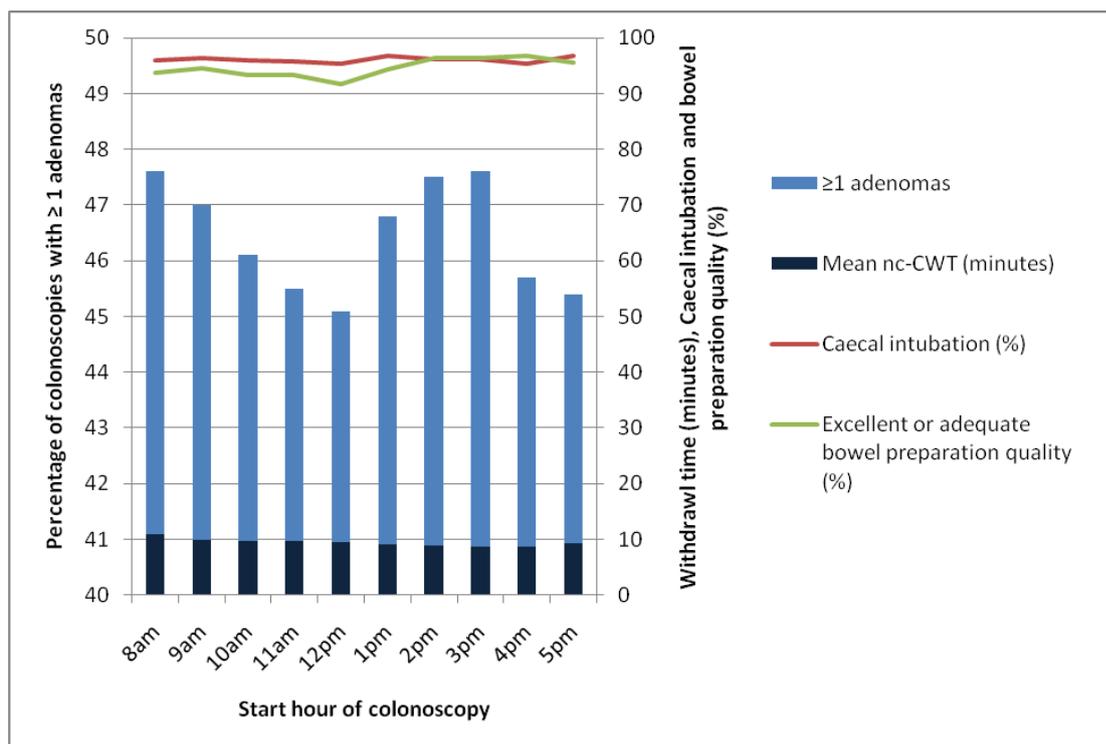


Figure 19- Relationship between start time of colonoscopy and adenoma detection, withdrawal time, caecal intubation and bowel preparation quality

The ordinal regression model demonstrating the relationship between the total number of adenomas detected at each colonoscopy and patient and colonoscopy factors is shown in table 32. Only significant factors are displayed. The odds ratio refers to the odds of the group having more adenomas in total than the reference group.

	Odds Ratio	95% confidence interval	Significance (p)
Gender			
Female	1.89	1.78-1.99	<0.001
Male	1.00	-	-
Age (years)			
<62.5	0.75	0.70-0.80	<0.001
62.5-64.9	0.82	0.76-0.88	<0.001
65-67.49	0.90	0.84-0.96	0.003
≥67.5	1.00	-	-
Smoking			
Never	0.55	0.51-0.60	<0.001
Ex-smoker	0.64	0.59-0.70	<0.001
Current smoker	1.00	-	-
Alcohol			
No	0.76	0.72-0.81	<0.001
Yes	1.00	-	-
Caecal Intubation			
No	0.24	0.19-0.27	<0.001
Yes	1.00	-	-
Rectal retroversion			
No	1.34	0.82-0.68	<0.001
Yes	1.00	-	-
Mean nc-CWT (minutes)			
<10	0.89	0.84-0.93	<0.001
≥10	1.00	-	-
Bowel preparation quality			
Inadequate preparation	0.70	0.63-0.79	<0.001
Excellent or adequate	1.00	-	-
Hyoscine use			
No	0.76	0.73-0.80	<0.001
Yes	1.00	-	-
Start time of procedure			
8-10.59 am or 2-3.59pm	1.08	1.03-1.13	0.003
11am-1.59pm or 4-5.59pm	1.00	-	-
Prior colonoscopist experience in the BCSP (number of procedures)			
0-299	0.81	0.75-0.88	<0.001
≥300	1.00	-	-

Table 32- Ordinal regression model of the effect of patient and colonoscopy factors on the total number of adenomas detected per procedure.

3.3.4- Discussion

This is the largest study examining the relative effect of both patient and colonoscopist factors on adenoma detection in an FOB test screened population. Patient factors including male gender, increasing age, smoking and alcohol use are shown to be associated with increased detection of one or more adenomas, advanced adenomas and right sided adenomas. Increasing deprivation is shown to have an inverse association with adenoma detection. With these variables taken into account, a geographical variation in adenoma detection within England is seen. Colonoscopy factors are also shown to have an important effect on adenoma detection. Caecal intubation and bowel preparation quality have the strongest association with increasing adenoma detection. Longer mean withdrawal time of the colonoscopist, intravenous antispasmodic drug use, earlier start time of the procedure and prior colonoscopist experience are all shown to significantly increase adenoma detection. Rectal retroversion is not associated with an increase in adenomas or rectal adenomas. This study also demonstrates the finding that these factors have similar associations with advanced adenoma and right sided adenoma detection.

This study has important implications for colonoscopy practice. We recommend routine use of intravenous antispasmodic medication, mean negative complete withdrawal time greater than 10 minutes and judicious use of rectal retroversion. Further investigation of the causes of reduction in adenoma detection as a session progresses is required to ameliorate this phenomenon.

Patient factors

Gender, age and lifestyle factors are well recognised risk factors for colorectal neoplasia as demonstrated by a recent analysis of lifestyle factors on polyp detection in the USA (Hassan et al 2010). 1,321 asymptomatic adults underwent primary screening colonoscopy and same-day CT colonography showing a positive association between male gender, BMI ≥ 25 kg/m² and increasing age with colorectal neoplasia. Other lifestyle factors including smoking and alcohol consumption were not shown to be associated with neoplasia detection; this may be a result of under-powering due to the relatively small sample size. Our study confirms that male gender, increasing age, smoking (or being an ex-smoker) and alcohol use are important risk factors for adenoma detection. Figure 18 demonstrates this relationship and the finding

that within the study population, females who smoke and drank alcohol had a higher risk of adenoma detection (47.8%) than males who didn't smoke or drink (44.8%, $p < 0.001$). These findings are clinically relevant and should direct clinicians to inform patients of the risks associated with lifestyle choices.

No statistically significant relationship between BMI and adenoma detection was demonstrated, however, slightly more adenomas were detected in individuals with a BMI greater than 25. This reflects the inconsistent findings on the role of BMI as a risk factor for colorectal neoplasia in the existing literature. A study of 3,121 (predominately male) individuals in the USA undergoing colonoscopy did not show any association between BMI and risk of advanced adenoma detection (Lieberman et al 2000). Other studies however, have shown an association between increasing BMI and increased risk of colorectal neoplasia both in the general population and in those undergoing screening colonoscopy (Giovannucci et al 1995; Hassan et al 2010; Betes et al 2003). The findings of the current study regarding BMI are potentially limited by the higher rate of missing data for this variable and the reliance on self reported measures of height and weight.

An inverse relationship between deprivation and adenoma detection was seen. In the multivariable model, decreasing deprivation was associated with a 15% increase in adenoma detection. It is known from the pilot study of CRC screening in the UK that uptake of screening is lower in more deprived areas (uptake varied from 61.2% to 37.2% in IMD quintiles 1–5 respectively (test for trend $p < 0.001$) (Weller et al 2004). Similar findings were noted in the Nottingham randomised controlled trial of FOB screening (Whynes et al 2003). It is also known that colorectal cancer incidence is higher in those who don't take up the offer of screening compared to those who do (Niv et al 2002). A potential explanation therefore, is that individuals who take up the offer of screening in more deprived areas differ from those who don't take up the offer of screening but who harbour more neoplasia. In less deprived areas, where uptake is higher, this effect is reduced and adenoma detection is not diluted. Other possible factors we are unable to account for include differences in diet, physical exercise and the potential for there to be more false positive FOB tests in the lower socioeconomic groups (perhaps due to differing patterns of non steroidal anti-inflammatory medication use). A limitation of this analysis is the use of area-level rather than individual measures of socioeconomic status.

A geographical variation in adenoma, advanced adenoma and right sided adenoma detection was shown to exist even when available patient and colonoscopy variables are adjusted for. This variation may be the result of regional variation in the underlying prevalence of colonic adenomas in England. A regional variation in colorectal cancer incidence has also been observed (Cancer Research UK 2011). Alternatively, it may reflect variations in colonoscopic performance or biological risk factors which have not been accounted for. The geographical variation in adenoma detection requires further investigation.

Colonoscopy factors

Caecal intubation is, unsurprisingly, strongly associated with adenoma detection. An alternative approach to our method of analysis would be to exclude incomplete procedures. Doing so resulted in minimal change to the outcome of the models but reduced the size of the study population.

Adenomas were more likely to be detected where the bowel preparation was better. Improving bowel preparation quality is a widely accepted way of improving adenoma detection (Froelich et al 2005; Belsey et al 2007). A standardised bowel preparation protocol is not used in the NHS BCSP, the bowel preparation used for each individual colonoscopy was not available for analysis, therefore we cannot comment on the use or timing of different bowel preparations in this study.

Rectal retroversion is not shown to increase detection of either adenomas or rectal adenomas. Surprisingly, it is associated with a reduction in detection of advanced adenomas. A potential explanation for this unexpected finding is that rectal retroversion is less likely to be performed if significant pathology has already been detected earlier in the procedure. It is currently recommended that rectal retroversion is performed during colonoscopy in the NHS BCSP (Chilton et al 2011). This recommendation is based on a study of 480 screening flexible sigmoidoscopies which showed an absolute increase of 1% in number of adenomas detected when rectal retroversion was performed (Hanson et al 2002). A more recent US study showed that rectal retroversion did not detect clinically important neoplasia after careful forward viewing examination and emphasised the potential discomfort and harm of the manoeuvre (Saad et al 2008). Data presented in section 3.1.3 of this thesis suggest a

modest positive correlation between rectal retroversion rate and ADR. This may appear at odds with the findings in the current study. However, the correlation between RRR and ADR is likely explained by the fact that colonoscopists with higher ADR are more likely to perform rectal retroversion. The current study examines the relationship at the 'per procedure' level and demonstrates no increase in adenoma detection with rectal retroversion.

Rectal retroversion may be a particularly uncomfortable phase of the colonoscopy for the patient and has risks associated with it including bleeding and perforation, particularly if the rectum is inflamed. The majority of the distal rectum can be adequately examined with the increased field of view of a modern colonoscope in the forward viewing position. Anecdotal reports mention the presence of lesions which can only be seen on retroversion though this is a rare phenomenon. On the basis of the lack of evidence for increased lesion detection compared to the potential for discomfort or harm to the patient, we conclude that performance of rectal retroversion should not be used as a quality indicator of screening colonoscopy. We agree with the authors of the US study that use of rectal retroversion should be at the discretion of the colonoscopist. Thorough colonoscopic inspection of the distal rectum remains an essential part of the examination.

Colonoscopists with a mean (negative complete) colonoscopy withdrawal time (nc-CWT) detected one or more adenomas in 10% more individuals than colonoscopists with a mean nc-CWT of less than 10 minutes. Longer withdrawal time is also associated with increased detection of right sided adenomas but no increase in advanced adenoma detection was seen. Advanced adenomas, which are likely to be larger than 1cm in size, are likely to be detected even with shorter withdrawal times. We encourage screening colonoscopists to aim for a mean nc-CWT of around 10 minutes.

Intravenous hyoscine n-butyl bromide use is associated with a 30% increase in adenoma detection. This holds true for advanced adenomas and right sided lesions. It is not clear if the administration of the antispasmodic is responsible for the increase in adenoma detection or if antispasmodic use is a feature of higher performing colonoscopists. Existing literature is conflicting on the role of antispasmodic use during colonoscopy in terms of procedure time and patient comfort (Saunders et al 1996; Mui et al 2004). Data on adenoma detection and antispasmodic use is limited. A recent small South Korean study of 116 patients showed a non-significant increase in adenoma detection in patients with high colonic spasm scores with hyoscine use (1.21 polyps per patient in the group given hyoscine vs. 0.41 in the placebo

group, $p=0.06$) (Lee et al 2010). A randomised controlled trial of intravenous antispasmodic use in the screening setting is required.

Time of day of colonoscopy has previously been shown to affect adenoma detection. Two US studies have demonstrated that polyp detection decreases in afternoon compared to morning colonoscopies and with each subsequent hour of the day (Sanaka et al 2009; Chan et al 2009). Analysis of adenoma detection in the BCSP by hour of the day is shown in figure 19. The pattern appears to reflect working practice in England where colonoscopy is performed during morning (8am or 9am to 1pm) or afternoon (2pm to 5pm) lists and colonoscopists tend not to perform all-day lists. When colonoscopies are divided into two groups, those towards the start of a list (8-11am and 2-4pm) and those towards the end of a list (11-2pm and 4-6pm), a decrease in detection of one or more adenomas or advanced adenomas of around 6% is demonstrated. Bowel preparation scores, caecal intubation rate and normal complete withdrawal time are all adjusted for in this analysis. Although we have no evidence to directly support the theory, colonoscopist fatigue may be contributing to this reduction in adenoma detection. A recent single centre US study of 20 colonoscopists has observed a similar phenomenon of declining polyp detection toward the end of an endoscopist's shift (Long et al 2011).³⁷ Screening colonoscopists should reflect on their own practice to minimise the effect of fatigue during a colonoscopy list. Further investigation into the potential role of operator fatigue during colonoscopy is required.

Previous reports on the effect of colonoscopist experience on adenoma detection are conflicting. A number of studies show no relationship or a negative association between increasing experience and adenoma detection (Barclay et al 2006; Chen et al 2007; Simmons et al 2006). A study of adenoma detection in a large trial of flexible sigmoidoscopy screening demonstrated that the adenoma detection rate of some endoscopists increased with experience (Atkin et al 2004). Our data suggests that individuals colonoscoped by a colonoscopist who had performed ≥ 300 colonoscopies in the screening programme were 1.2 times more likely to have one or more adenomas than if the colonoscopist had performed < 300 procedures. It should be noted that procedures performed by colonoscopists who had performed less than 50 procedures were not included in this analysis. It is likely that experience within the screening programme is important.

Unsedated colonoscopy comprised 13.1% of screening colonoscopies in our study. Two US studies have suggested that deeper sedation is associated with increasing detection of colonic pathology (Radaelli et al 2008; Wang et al 2008). Our data provide reassuring evidence that adenoma detection is not reduced in patients undergoing unsedated colonoscopy.

Analysis of the total number of adenomas detected echoes the findings when the outcome variable is one or more adenomas. The strongest associations between patient factors and increasing number of adenomas are for being male and increasing age. Hyoscine use, earlier start time and colonoscopist experience (>300) are all associated with increasing numbers of adenomas detected. Once again, rectal retroversion not being performed is associated with increasing numbers of adenomas detected. As discussed previously, this may be because a colonoscopist is less likely to perform retroversion when multiple polyps have been detected,

Our study has a number of limitations. Firstly, data were not available on some notable patient risk factors including family history of colorectal cancer and aspirin use. Secondly, this study is retrospective in design and lacks the advantages of a prospective randomised controlled trial. However, data for this study were collected prospectively and the size and breadth of the dataset offset some of these limitations.

Finally, many statistically significant relationships are seen in the dataset. This reflects both the relationships between the study variables and the size of the dataset. The clinical relevance of certain findings is less clear, however, even small odds ratios (such as ≥ 1 adenoma detection in late vs. early start time of colonoscopy, OR= 0.94 (0.90-0.99), $p=0.018$) may have important clinical implications, both at a population level and for individual patients, colonoscopist and screening centres.

In summary, this large study of over 31,000 colonoscopies by 148 colonoscopists in the NHS Bowel Cancer Screening Programme, demonstrates the importance of both patient and colonoscopy factors in determining the risk of an adenoma being detected during screening colonoscopy. In particular, the study draws attention to factors which the patient may modify in order to minimise their risk of having an adenoma (smoking and drinking alcohol) and also to factors which the colonoscopist may modify in order to optimise adenoma detection (caecal intubation, mean withdrawal time, bowel preparation quality and start time of the colonoscopy). These factors affect not only the risk of detecting one or more adenomas but also advanced adenomas and right sided adenomas. Many of the colonoscopy factors shown to affect adenoma detection in this study have been proposed as contributing to the risk of

missing lesions during colonoscopy, increasing the risk of post colonoscopy colorectal cancer (Rex 2000; Rabeneck et al 2010; Bressler et al 2007). This may be particularly relevant to right sided lesions which are harder to detect and potentially biologically different to left sided lesions (Singh et al 2006; Nawa et al 2008; Arain et al 2010). Awareness of the effect of these factors may contribute to reducing the risk of colonoscopy missing adenomas and subsequent interval pathology.

Chapter 4- Management of colorectal neoplasia in the NHS Bowel Cancer Screening Programme

Chapter 4.1- Outcome of 12 month surveillance colonoscopy in high risk patients in the NHS Bowel Cancer Screening Programme

4.1.1- Introduction

Surveillance colonoscopy is recommended for individuals who have previously had adenomas removed as the risk of having further adenomas is up to 50% (Waye et al 1992; Atkin et al 1992, Winawer et al 1993). The aim of surveillance colonoscopy is to prevent subsequent colorectal cancer. Most small adenomas will not progress to malignancy, however, adenomas larger than 1cm in size or displaying high grade dysplasia are known to have greater malignant potential (Eide 1986). Such lesions are termed ‘advanced adenomas’ and the presence of these lesions is widely used as an outcome measure in studies of colonoscopic surveillance.

The risk of having further adenomas detected at surveillance is dependent on the characteristics of the adenomas removed at baseline (Martinez et al 2001). The presence of multiple adenomas (greater than 3), especially if one or more is larger than 1cm in size, is associated with an increased risk of detecting advanced adenoma or cancer at surveillance (Noshirwani et al 2001; Saini et al 2006; Martinez et al 2009). A recent pooled analysis of risk factors for finding adenomas at surveillance colonoscopy identified the presence of advanced adenoma, 3 or more adenomas, an adenoma ≥ 10 mm in size and age ≥ 60 years as the most important risk factors for detection of adenomas at surveillance (de Jonge et al 2011).

The British Society of Gastroenterology guidelines on surveillance following detection of adenomas define individuals with 3 or more adenomas of which one is ≥ 10 mm in size or five or more adenomas of any size, as being at high risk of having further advanced adenomas or cancer detected and recommend that they should undergo surveillance colonoscopy 12 months following the baseline procedure (Atkins et al 2002; Cairns et al 2010).

The NHS Bowel Cancer Screening Programme has adopted the BSG guidelines on adenoma surveillance (opting for ongoing biennial FOB screening for the low-risk group rather than 5 year surveillance colonoscopy). The surveillance programme operates within the auspices of the BCSP. All subsequent surveillance procedures are therefore subject to the same quality assurance standards of screening colonoscopy (see chapter 1.1)

This study has two main objectives. Firstly, to describe the findings at 12 month surveillance colonoscopy in high risk individuals in the BCSP. Secondly, to identify baseline patient and clinical characteristics which may predict an individual's risk of having advanced adenoma or cancer (collectively termed advanced colonic neoplasia; ACN) at surveillance.

4.1.2- Method

Study Population

Demographic, colonoscopic and histological data on all individuals undergoing colonoscopy in the NHS BCSP were prospectively recorded in a national database. The outcome of colonoscopy in individuals found to have adenomas was recorded as either low risk, high risk or intermediate risk according to the criteria in the BSG guidelines on adenoma surveillance (Atkins et al 2002). We identified individuals who were assigned to the high risk group as a result of the baseline screening episode between August 2006 and April 2010. The indication for surveillance colonoscopy in this group was detection of 5 or more adenomas smaller than 10mm or three or more adenomas of which at least one was 10mm or greater in size during colonoscopy in the screening episode. Individuals who did not go on to have surveillance colonoscopy or who did not fulfil the high risk BSG guideline criteria were excluded.

All individuals underwent colonoscopy in the baseline screening episode as a result of a positive faecal occult blood test. Individuals may have had more than one colonoscopy or flexible sigmoidoscopy within a screening episode (if the bowel preparation quality was poor or further therapeutic procedures were required).

Study procedures

Demographic and lifestyle data (date of birth, gender, smoking status, alcohol consumption, height (metres), weight (kg), were collected from individuals prior to colonoscopy in the

NHS Bowel Cancer Screening Programme. These data were recorded on the BCSP national database to which colonoscopy data were added at the time of the procedure. Histological data for any lesions detected at colonoscopy were also recorded on the database. Data were downloaded from the national database in August 2010 for cleaning and analysis. Where possible, missing data were obtained from the screening centre.

Age was recorded on the date of the first colonoscopy in the screening episode rather than at entry to the screening programme. Smoking status was categorised as current smoker, ex-smoker or never smoked. Alcohol use was categorised as either current use or not. Patient body mass index (BMI, kg/m²) was calculated from height and weight measurements

Screening and surveillance colonoscopic findings and histopathological results were also obtained from the national database.

Baseline screening colonoscopic findings were categorized as 3 or more small adenoma of which at least one was 10mm or greater in size, 5 or more small (<10mm) adenomas or 5 or more adenomas of which at least one was 10mm in size. The presence of one or more advanced adenomas, adenomas with a villous component or adenomas displaying high grade dysplasia was also recorded.

Surveillance colonoscopic findings were categorised by the presence of one or more lesions displaying advanced colonic neoplasia (ACN). Details of the Dukes Stage and site of cancers detected at surveillance colonoscopy were checked with the local screening centre.

In order to examine whether the colonoscopic quality of the screening colonoscopist affected the findings at 12 month surveillance, we included the adenoma detection rate (ADR) of the screening colonoscopist as a continuous variable in the univariable analysis. ADR was calculated based on all first screening colonoscopies performed by the colonoscopist between August 2006 and August 2009. Colonoscopists who had performed less than 50 procedures in this period were excluded from this part of the analysis because of the inaccuracy of ADR when fewer than 50 procedures have been performed.

Statistical Analysis

Data were analysed using SPSS (v10.0, Chicago, Illinois, USA). Continuous variables are presented as mean (standard deviation (sd)) if normally distributed or median (interquartile

range) if their distribution is skewed. Categorical variables are presented as number (%). Where two proportions are compared, a two tailed test of two proportions was used.

Age, BMI, interval to surveillance (days) and ADR of screening colonoscopist were analysed as continuous variables. Univariable testing was undertaken with the χ^2 test for categorical variables and the unpaired T test for normally distributed continuous data. All tests were 2 tailed and a p value of <0.05 was considered significant.

Multivariable binary logistic regression modelling was undertaken to examine the relationship between baseline colonoscopic findings and presence of advanced neoplasia at surveillance colonoscopy. In order to avoid excluding factors with marginal effect, variables were included in the model if a p value of <0.1 was present in univariable analysis. Odds ratios with 95% confidence intervals were calculated for significant variables in the model.

4.1.3- Results

Participants

1760 individuals underwent colonoscopy in the screening episode following a positive FOB test and subsequently had surveillance colonoscopy around 12 months later.

1340/1760 (76.1%) individuals undergoing 12 month surveillance were male compared to 61.6% of individuals undergoing colonoscopy in the screening programme as a whole (p<0.001). This suggests males are more likely to fall into the high risk group at baseline. The mean age at baseline colonoscopy of individuals subsequently undergoing 12 month surveillance was 65.8 years (sd 3.5). This is similar to the mean age of all patients undergoing colonoscopy in the programme (65.8 years (sd 3.74), p=0.526).

The mean interval between first colonoscopy in the screening episode and surveillance colonoscopy was 387 days (sd 89 days). 1637/1760 (93.0%) of surveillance procedures were completed within 3 months of the 'due date' (365 days after the baseline screening colonoscopy). 1294/1760 (73.5%) patients had more than one procedure during the screening episode due to the need for endoscopic therapy or poor bowel preparation necessitating a further procedure.

Surveillance colonoscopy

The yield of surveillance colonoscopy at 12 months for cancer was 0.8% (14/1760, equivalent to 7.5 cancers per 1000 person years of observation, PYO), the yield for advanced adenomas was 6.1% (108/1760, 58.1 cases per 1000 PYO). The yield of advanced colonic neoplasia (ACN- a composite of the previous two outcomes) was 6.6% (116/1760, 62.4 ACN per 1000 PYO), 6 patients with both an advanced adenoma and cancer at surveillance were only counted once.

866/1760 (49.2%) of individuals had no adenomas and 778/1760 (44.2%) had one or more non-advanced adenomas detected at 12 month surveillance. 62/1760 (3.5%) had 5 or more adenomas detected at 12 months.

Baseline characteristics

The demographic and lifestyle factors of those with and without ACN at surveillance are shown in table 33. No significant differences were seen between the two groups in age, gender, smoking status, alcohol use, BMI, number of screening procedures or interval from baseline to surveillance colonoscopy.

Findings at baseline screening colonoscopy in the two groups were compared. These are shown in table 34.

	Total n=1760	No ACN at Surveillance n= 1644 n (%) or mean (sd)	≥1 ACN at surveillance n=116 n (%) or mean (sd)	Significance (p value)
Age (years)				
mean (sd)	65.8 (3.5)	65.8 (3.5)	65.9 (3.4)	0.917
Gender				
Male (%)	1340 (76.1)	1251 (93.4)	393 (93.6)	1.000
Smoking* (n,%)				
Non smoker	743 (42.2)	697 (93.8)	46 (6.2)	0.660
Ex-smoker	701 (39.8)	655 (93.4)	46 (6.6)	
Current	311 (17.7)	287 (92.3)	24 (7.7)	
BMI (m/kg²)[#]				
mean (sd)	28.0 (5.9)	28.0 (5.9)	28.6 (6.6)	0.353
Alcohol use[~] (n,%)				
No	422 (24.0)	391 (92.7)	31 (7.3)	0.501
Current	1327 (75.4)	1242 (93.6)	85 (6.4)	
Number of procedures in screening episode				
1	1294 (73.5)	1215 (93.9)	79 (6.1)	0.191
>1	466 (26.5)	429 (92.1)	37 (7.9)	
Interval between last screening and first surveillance procedure (days)				
Mean (sd)	384.9 (86.7)	385.4 (85.8)	389.5 (93.4)	0.650

Table 33- Patient and colonoscopist characteristics in those with no ACN compared to those with one or more ACN at 12 month surveillance colonoscopy.

* Smoking status unknown in 5 patients

BMI unknown in 218 patients

~ Alcohol use unknown in 11 patients

	Total n=1760	No ACN at Surveillance n= 1644 n (%) or mean (sd)	≥1 ACN at surveillance n=116 n (%) or mean (sd)	Significance (p value)
Adenomas detected at screening colonoscopy				
≥3 adenomas, ≥1 larger than 10mm	997 (56.6)	938 (94.1)	59 (5.9)	0.412
≥5 adenomas (all <10mm)	144 (8.1)	134 (93.1)	10 (6.9)	
≥5 adenomas, ≥1 larger than 10mm	619 (35.2)	572 (92.4)	47 (7.6)	
Presence of advanced adenoma				
None	228 (13.0)	212 (93.0)	16 (7.0)	0.775
≥1	1532 (87.0)	1432 (93.5)	100 (6.5)	
Presence of Villous adenoma				
None	1634 (92.8)	1533 (93.8)	101 (6.2)	0.023
≥1	126 (7.2)	111 (88.1)	15 (11.9)	
Presence of large adenoma (≥10mm)				
None	144 (8.2)	134 (93.1)	10 (6.9)	0.860
≥1	1616 (91.8)	1510 (93.4)	106 (6.6)	
Presence of very large adenoma (≥40mm)				
None	1604 (91.1)	1499 (93.5)	105 (6.5)	0.160
≥1	107 (6.1)	96 (89.7)	11 (10.3)	
Presence of high grade dysplasia				
None	1286 (73.1)	1196 (93.0)	90 (7.0)	0.280
≥1	474 (26.9)	448 (94.5)	26 (5.5)	
Presence of multiple adenomas (≥10)				
<10 adenomas	1666 (94.7)	1558 (93.5)	108 (6.5)	0.395
≥10 adenomas	86 (5.3)	86 (91.5)	8 (8.5)	
Presence of right sided adenoma				
None	606 (34.4)	579 (95.5)	27 (4.5)	0.008
≥1	1154 (65.6)	1065 (92.3)	89 (7.7)	
Adenoma Detection rate of screening colonoscopist				
ADR	48.3 (6.1)	48.0 (6.1)	47.1 (6.6)	0.126

Table 34- Baseline screening colonoscopy findings in those with and without ACN at 12 month surveillance colonoscopy.

There appeared to be a trend between the indication for surveillance colonoscopy according to the BSG adenoma surveillance criteria and yield of ACN at 12 months. 59/997 (5.9%) individuals with 5 or more small (<10mm) adenomas at baseline had ACN at surveillance compared to 10/144 (6.9%) individuals with 3 or 4 adenomas of which one \geq 10mm in size. 47/619 (7.6%) individuals with both 5 or more adenomas and one or more \geq 10mm in size had ACN at surveillance. This relationship was not significant ($p=0.412$).

The following baseline factors were not associated with the presence of ACN at surveillance colonoscopy: ≥ 1 advanced adenomas ($p=0.775$), ≥ 1 large (≥ 10 mm) adenomas ($p=0.860$), high grade dysplasia ($p=0.280$), ≥ 1 very large (≥ 40 mm) adenoma ($p=0.160$), multiple (≥ 10) adenomas ($p=0.395$).

The presence of one or more villous adenomas at baseline colonoscopy was associated with increased incidence of ACN at surveillance (101/1634 (6.2%) vs. 15/126 (11.9%), $p=0.023$). Also, the presence of one or more right sided adenomas at baseline was associated with ACN incidence at surveillance (27/606 (4.5) vs. 89/1154 (7.7%), $p=0.008$).

In multivariable analysis, the odds ratio for ACN detection at surveillance if ≥ 1 villous lesions were present at baseline was 1.98 (95% CI 1.11-3.53, $p=0.020$) and 1.76 (1.13-2.74, $p=0.012$) if ≥ 1 right sided adenoma were present.

There was no difference in mean adenoma detection rate per colonoscopist (for the screening colonoscopy) between those with and without ACN at surveillance (48.0% vs. 47.1%, $p=0.126$), indicating that within the BCSP, the technical quality of the index screening procedure was not a significant factor in the yield of ACN at surveillance colonoscopy.

Cancers detected at surveillance

Fourteen cancers were detected at surveillance colonoscopy. No synchronous cancers were detected. The site and Dukes stage of the cancers are shown in table 35. 6/14 (42.9%) of cancers were located in the right colon (proximal to the splenic flexure). 9/14 (64.3%) of the cancers were Dukes stage A at diagnosis. There was no association between site and increasing stage at diagnosis. One or more adenomas had been removed from the same segment of colon in which the cancer was subsequently detected in 9/14 (64.3%) cases. The largest adenoma in this segment was 10mm or greater in 5/8 (62.5%) cases. The size of the largest lesion at index colonoscopy was not known in one case.

	Site	Dukes stage	Number of polyps removed from the same segment at baseline screening colonoscopy	Size of largest polyp removed from this segment (mm)
1	Rectum	A	2	20
2	Rectum	A	0	-
3	Sigmoid colon	A	1	15
4	Sigmoid colon	A	4	25
5	Sigmoid colon	A	2	5
6	Sigmoid colon	A	1	Not known
7	Sigmoid colon	C1	1	10
8	Sigmoid colon	C2	0	-
9	Transverse colon	C2	2	4
10	Ascending colon	A	0	-
11	Ascending colon	A	2	10
12	Ascending colon	A	0	-
13	Ascending colon	B	1	2
14	Ascending colon	C1	0	-

Table 35- Characteristics of surveillance detected cancers

4.1.4- Discussion

This study of patients at high risk of future neoplasia based on colonoscopy findings following positive FOB screening demonstrated a yield at 12 month surveillance colonoscopy of 0.8% for colorectal cancer and 6.1% for advanced adenomas.

The rate of advanced colonic neoplasia of 6.6% justifies the need for 12 month surveillance interval in this high risk group of patients according to the current BSG guidelines for surveillance following adenoma detection.

Comparison of the incidence of advanced colonic neoplasia at surveillance in the current study with other published series of colonoscopic surveillance is limited by the highly selected nature of this subject population. Noshirwani et al (2000) report the occurrence of advanced adenoma (including villous lesions) at surveillance (within 3 years of baseline colonoscopy) in 15.3% of average-risk individuals with 4 or more small (<10mm) adenomas at baseline and 21.3% of individuals with 3 adenomas of which one was 10mm or greater in size. Martinez et al (2001) report advanced adenoma incidence within 3 years of baseline colonoscopy in 12.3% of average-risk individuals with 3 or more adenomas and 16.6% of individuals with a large (≥ 10 mm) adenoma. Although these studies are not directly comparable with our study, the incidence of ACN at 12 months is lower in our higher risk

(FOBT positive) population than the incidence of advanced adenomas in the average risk populations in the other two studies. It may be concluded that this is a consequence of higher quality baseline colonoscopy in our study. It is unlikely that the shorter surveillance interval in our study or difference in definition of advanced adenoma would account for the differences seen. This argument is countered by the rate of advanced adenomas at surveillance in our study being slightly in excess of miss rates of colonoscopy for lesions 1cm or greater in size determined by tandem colonoscopy studies (Rex et al 1997; van Rijn et al 2006). In addition, two recent chemoprevention studies have shown cancer rates during one to two years of follow up of 0.3 to 0.4% following colonoscopy (Arber et al 2006; Robertson et al 2005). These rates are lower than the 0.8% rate of cancer at 12 months seen in our study.

The study shows that patient characteristics including age, gender, smoking status, alcohol use and BMI are not associated with ACN incidence at 12 months. Within the high risk category, increasing number and size of adenomas and presence of high grade dysplasia at baseline screening colonoscopy are not associated with outcome at 12 months. The presence of one or more villous adenomas however, is associated with a nearly two fold increase in the risk of ACN detection at 12 months. Histological subtype (presence of villous architecture) is not a criterion for surveillance in the existing BSG guidelines on colonoscopic surveillance following adenoma detection. This is in part due to concerns regarding the subjective nature of pathological description of villousness for which there is considerable inter-observer variability (Constantini et al 2003). Other guidelines however, do include villousness as an indication for closer surveillance (Smith et al 2002; Bond et al 2000).

The presence of one or more right-sided adenomas at baseline colonoscopy was associated with a 1.76 fold increase in the risk of ACN detection at 12 months compared to individuals with only left sided adenomas. A pooled analysis of seven studies of outcome at surveillance colonoscopy suggested a pooled risk ratio of 1.43 (95% CI 1.30-1.57) for adenoma recurrence when any proximal adenoma was present (de Jonge 2010). It has been argued that colonoscopy is less effective in the proximal colon and as a result may not reduce the incidence of or mortality from proximal colorectal cancer (Baxter et al 2009; Brenner et al 2010).

The association of the presence of a right sided lesion with subsequent ACN may be explained by the propensity for right sided lesions to be more difficult to detect and therefore more likely to be missed at baseline colonoscopy (Singh et al 2009; Nawa et al 2008).

Alternatively, the association may be due, in part, to the differing biology of right sided compared to left sided colonic neoplasia (Arain et al 2010). This may account for more *de novo* lesions at surveillance colonoscopy.

Future studies of the outcome of one and three year surveillance colonoscopy in the Bowel Cancer Screening Program should investigate further the predictive role of villous adenomas and right sided adenomas as markers of risk for future ACN which may necessitate an addition or amendment to the existing guidelines.

This study has a number of other important conclusions. Firstly, patients who underwent repeated procedures during the screening episode did not have a different incidence of ACN at 12 months compared to those who had only one procedure in the screening episode. This suggests the need for repeated procedures during the screening episode does not confer any extra protection, due to repeated mucosal inspection, from ACN detection at 12 months. This may be explained by some of the initial procedures being suboptimal (due to poor bowel preparation or not reaching the caecum) necessitating a repeat procedure. In addition, mucosal inspection may not have been the primary objective of the repeat procedure, for instance if the objective of the repeat procedure was to remove a large polyp.

Secondly, the quality of the screening colonoscopist, as assessed by their overall adenoma detection rate, did not appear to affect the incidence of ACN at 12 months. This may be because the colonoscopists involved in the study were of a consistently high standard (the mean ADR per colonoscopist was 48.3%) and all colonoscopists are required to meet predefined standards and complete a directly observed assessment prior to commencing practice in the BCSP. An alternative explanation is that colonoscopists with higher ADR are more likely to find multiple or large adenomas resulting in a higher proportion of their patients requiring surveillance colonoscopy. For this reason, the association between the quality of the screening colonoscopist and the incidence of interval pathology will be difficult to assess. The use of interval cancer rate, as in a recent Polish study which demonstrated an association between lower ADR and higher interval cancer rates, may be more informative (Kaminski et al 2010).

Thirdly, cancers detected at 12 month surveillance colonoscopy had a favourable stage profile. 64.3% of these cancers were Dukes Stage A at diagnosis compared to 8.7% in the general population and around 45% in the Bowel Cancer Screening Programme (Ellul et al 2010; National Cancer Intelligence Network 2009). The favourable prognosis of interval

cancers has been observed in the colorectal cancer screening previously (Hardcastle et al 2006). Further research into the outcomes of patients with advanced adenomas at surveillance will identify if this group of patients are at ongoing high risk of developing neoplasia or if screening and early surveillance confer long-lasting protection.

A higher proportion of surveillance-detected cancers were located in the right colon (proximal to and including the splenic flexure) compared to the general population (42.9% vs. 31%) (Toms 2004). The majority of surveillance detected cancers (79%) were located in either the ascending or sigmoid colon. This may be explained by the fact that these areas of the bowel are more technically challenging to examine during withdrawal increasing the potential for missed lesions in these segments.

It is hazardous to attempt to determine whether lesions detected at surveillance were missed during screening, a result of incompletely resected lesions or *de novo* lesions arising during the surveillance interval. In our study, 9/14 (64.3%) cancers detected at 12 months were located in a segment in which an adenoma had been removed previously. According to a protocol described in a study by Pabby et al (2005) of colorectal cancers arising during surveillance, these would have been classified as arising due to incomplete resection. 4/13 (30.8%) of cancers in their study were classified in this group. Comparison with our study is limited by the higher baseline burden of adenomas in our study. This analysis can be extended to include site of the cancer, 3/6 (50%) patients with right sided cancers detected at surveillance had a polyp removed from the same segment in which cancer was subsequently found compared to 6/8 (75%) of patients with a left sided cancer. This raises the possibility that left sided cancers are more likely to have arisen from an incompletely resected lesion whereas right sided cancers are more likely to have been missed or new lesions. It is likely however, that at the majority of lesions detected at 12 months were present at the time of the baseline colonoscopy. There is an argument that the 12 month interval could be shortened to minimise the theoretical risk of advanced adenoma progressing to malignancy during the 12 month interval. A randomised controlled trial of 3 month versus 12 month surveillance in this group of patients would be valuable. The current European Union guidelines on colorectal cancer screening recommend surveillance colonoscopy *within* 12 months for individuals with 5 or more adenomas or an adenoma ≥ 20 mm to check for missed synchronous lesions (Segnan et al 2011). Our study supports the approach adopted by the European guidelines. Adoption of the European guidelines in the BCSP would result in numerically more

individuals meeting the high risk criteria. In a cohort of 31,088 individuals undergoing screening in the BCSP, 4331 (13.9%) met the European criteria for being high risk. In the same cohort, 2357 (7.5%) met the current high risk criteria.

This study has a number of limitations. Firstly, the relatively low incidence of ACN at 12 months limited the statistical analysis of predictive factors in the current sample size. It is possible that in a larger study, significant relationships between baseline characteristics and findings at 12 months may emerge.

Secondly, because the study population was confined to 60 to 69 year old adults with positive faecal occult blood testing, the external validity of the study may be limited. It is likely however, that individuals with high adenoma burden at index colonoscopy in the non-screening population have a similar risk of having further advanced adenomas in the future as the high risk screened population.

In conclusion, this study demonstrates that patients with a high adenoma burden at baseline screening colonoscopy have a 6.6% risk of advanced adenoma or cancer being detected at 12 month surveillance colonoscopy. This justifies the need for this surveillance interval in this high risk group of patients. The only baseline characteristics associated with increased risk of advanced colonic neoplasia being detected at 12 months were the presence of a right sided or villous adenoma. The favourable stage profile of cancers detected at 12 months is reassuring.

Chapter 4.2- Management of Large Sessile or Flat Colonic Polyps in the NHS Bowel Cancer Screening Programme

4.2.1- Introduction

The management of large sessile or flat colonic polyps (LSCP) is of clinical importance due to the potential of such lesions to harbour malignancy and their propensity to recur or progress to cancer if incompletely removed (Saito et al 2001). In addition, the management of LSCPs is associated with an increased risk of major complications to the patient (Heldwein 2005).

Such lesions, defined here as sessile or flat lesions (Paris classification 1s, 0-IIa, 0-IIb, figure 20) of 20mm or greater in size, may be managed endoscopically or surgically. Traditionally, surgery has been the mainstay for management of LSCPs (Voloyiannis et al 2008; Onken et al 2002), however endoscopic techniques have progressed to allow the removal of such polyps. Recent endoscopic techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have facilitated this progress (Swan et al 2009).

No consensus or formal guidelines exist for the choice of therapeutic modality (Metz et al 2011). In experienced hands both approaches seem to be acceptable (Church 2003).

Endoscopic management is associated with cost savings when compared to surgical management (Swan et al 2009), however, endoscopic management by non experts may be associated with worse outcomes (Brooker et al 2002).

The advent of laparoscopic colorectal surgery has made surgical management of large polyps less invasive and potentially safer than open surgery. The management of large or complex rectal lesions has been advanced by the development of Trans-anal Endoscopic Micro-Surgery (TEMS) which allows the removal of rectal lesions without a skin incision (Middleton et al 2005). However, surgery for colonic polyps remains associated with significant morbidity and mortality (Young-Fadouk et al 2000).

The advent of the English NHS Bowel Cancer Screening Programme (BCSP) in 2006 has led to an increased awareness of issues surrounding management of LSCPs through increased communication between screening endoscopists and the need for quality assurance of all steps of the screening pathway.

The aim of this study was to determine the incidence of such lesions in the BCSP and describe their current management and clinical outcome.

Endoscopic appearance	Paris class		Description
Protruded lesions	Ip		Pedunculated polyps
	Ips		Subpedunculated polyps
	Is		Sessile polyps
Flat elevated lesions	O-IIa		Flat elevation of mucosa
	O-IIa/c		Flat elevation with central depression
Flat lesions	O-IIb		Flat mucosal change
	O-IIc		Mucosal depression
	O-IIc/IIa		Mucosal depression with raised edge

Figure 20- Paris workshop guidelines for the morphological classification of colorectal lesions (Paris Workshop Participants 2002)

4.2.2- Methods

Study Population

All colonoscopies and flexible sigmoidoscopies performed in the NHS Bowel Cancer Screening programme (BCSP) between August 2006 and April 2009 were analysed. Data were collected between May and September 2010, thus allowing a minimum 12 month follow up period.

Study Procedures

Demographic, colonoscopic and histological data on all patients undergoing colonoscopy in the NHS Bowel Cancer Screening Programme are prospectively collected for quality assurance purposes. These data are stored in the Bowel Cancer Screening System (BCSS), a centrally maintained national database. Details of each polyp removed during colonoscopy in the BCSP is recorded in the BCSS, these data include the size, morphology, site and histological characteristics of the polyp. These data are recorded at the time of the procedure by a trained specialist screening nurse present in the endoscopy room and based on the colonoscopist's assessment of the lesion. Histological data are subsequently uploaded to the database. Both the endoscopist's assessment and the pathological assessment of the size of the lesion are recorded in the database.

The BCSS database was interrogated to identify polyps 20 mm or greater in size with flat or sessile morphology. Lesions were included if either the endoscopic or histological measurement of size was 20 mm or greater. 20mm was felt to be a clinically relevant cut-off as the management of lesions smaller than this is almost always endoscopic and the risk of malignancy or complications is smaller (Heldwein 2005). Pedunculated lesions were not considered in this study as their management differs to that of flat or sessile lesions. Our study focused on lesions which were initially clinically or histologically assessed as benign: lesions which were considered initially to be malignant were excluded as the management of malignant polyps is subject to other variables such as depth of invasion and risk of loco-regional spread. Likewise, patients were excluded if they had synchronous cancer, on the basis that the cancer rather than the LSCP would determine patient management. Where a patient had more than one LSCP, only the largest polyp or the polyp that determined clinical management was included in the study.

Detailed data on the management and follow up of patients with LSCP identified were obtained from the BCSS database and from the local screening centre where locally held medical records were reviewed to provide this information. Data were collected on the site and dysplastic grade of lesions, initial management modality (endoscopic or surgical) and subsequent management of the polyp. For surgically managed polyps, the indication for surgery, type of operation (including whether the operation was open or laparoscopic), length of stay for the operation and any surgical complications were recorded. For endoscopically managed polyps, details of the first therapeutic procedure, the total number of endoscopic

procedures up to the first surveillance procedure and any endoscopic complications were recorded. The majority of lesions managed endoscopically were managed with endoscopic mucosal resection (EMR). This technique involves submucosal injection of a saline or colloid solution under the lesion to facilitate safe snare resection of the lesion either in one piece (en bloc) or by a series of snare resections (piecemeal) (method described in Swan et al 2009).

Diathermy is employed to remove the polyps, the submucosal cushion is thought to provide a barrier to minimise thermal and mechanical trauma to the colonic wall. The term 'EMR' encompasses a spectrum of endoscopic techniques based on the principle outlined above. We have used the term 'endoscopic' management to encompass variations in the approach to EMR and other methods of polypectomy.

Within this study, the choice of initial management modality for each polyp was made by the clinician responsible for the patient, therefore variations in clinical practice occurred. For example, in some cases, lesions were removed when first discovered, whereas some endoscopists deferred formal endoscopic resection, taking biopsies from the lesion to provide pre-therapeutic histology. For the purpose of this study we have reported the initial histology as either the pre-therapeutic histology from biopsies or, where biopsies were not taken, the initial resection specimen.

Approval of this study as service evaluation was obtained from a Regional Ethics Committee. Individual patient consent for inclusion in the study and formal ethical approval were therefore not sought.

Data Analysis

Analysis was based on the first therapeutic modality employed for the management of each lesion (endoscopic or surgical). Age and gender of patient and site, size and histological nature of the lesions in each of these groups were compared.

The following outcomes were examined for all lesions:

1. The presence of malignancy in the endoscopic or surgical resection specimen

The definition of malignancy included adenocarcinoma and polyp cancers (lesions with malignant invasion through the submucosa but not beyond the muscularis mucosae).

2. Incidence of complications (endoscopic or surgical)

In the endoscopically managed group, the following outcomes were also analysed:

1. Need for surgery

- a. Due to detection of malignancy in the endoscopic resection specimen
- b. Because the lesion was no longer amenable to endoscopic management

2. Presence of residual or recurrent polyp (RRP) at 12 months

RRP was defined as endoscopically visible or microscopic evidence of polyp at the site of the index LSCP.

Patient factors (age, gender), LSCP characteristics (site, size and histological type) and endoscopic technique (en bloc or piecemeal resection) were assessed as potential factors for predicting the presence of malignancy, incidence of RRP at 12 months and subsequent need for surgery. Differences in management practice between individual screening centres were also explored.

Statistical Methods

Continuous variables are presented as mean (standard deviation (sd)). Categorical variables are presented as number (%). Where two proportions are compared, a two tailed test of two proportions was used. Categorical variables were compared with the χ^2 test. Parametric continuous variables were compared with the unpaired T test. Relative risks (RR, 95% confidence interval) were calculated for categorical variables and the appropriate outcome variable to demonstrate the strength of the association. All tests were 2 tailed and a p value of <0.05 was considered significant. Data were analysed using SPSS (v10.0, Chicago, Illinois, USA) and Stata (version 10, Statacorp, Texas USA).

4.2.3- Results

Patient and polyp characteristics

In the study period, 26,552 individuals underwent colonoscopy following a positive FOBt in the NHS BCSP, during which 40,704 polyps were detected. 868 lesions were identified in the BCSS national database as being 20mm or larger in size and flat or sessile in morphology.

Further data were obtained from the local screening centre for 807 (93.0%) of these lesions. Eighty two of the lesions were not 20mm or greater in size or flat or sessile according to locally held data at the screening centre, therefore these lesions were excluded. Thirteen lesions were identified as duplicate entries. 121/712 (17.0%) were assessed to be malignant on initial clinical or histological assessment and these were also excluded. 591/26552 (2.2%) individuals were therefore confirmed to have at least one LCSP. Thirty three patients were excluded due to the presence of a synchronous cancer. One 69 year old male patient was found to have a 3 cm sessile lesion in the caecum, pre-therapeutic histology showed a tubulovillous adenoma with high grade dysplasia. He declined surgery or further colonoscopy. This case was excluded from further analysis. 557/26552 (2.1%) lesions were therefore included in the main analyses.

These lesions were analysed according to the first therapeutic modality employed in their management. The characteristics of the patients and the lesions in each group are shown in table 36. The groups were similar in terms of age and gender distribution.

Lesions managed surgically were larger than those managed endoscopically (mean size 37.9mm vs. 29.5mm, $p < 0.001$). Right sided lesions were defined as those proximal to the splenic flexure. Left sided lesions were those at the splenic flexure or distal. 57/174 (32.8%) lesions in the right colon were managed surgically compared to 64/383 (16.7%) of those in the left colon ($p < 0.001$).

	Total	Endoscopic management	Surgical management	
Number n, (%)	557	436 (78.3%)	121 (21.7%)	
Mean age years, (sd)	66.4 (3.62)	66.4 (3.62)	66.7 (3.60)	P=0.296
Male n, (%)	384 (68.9%)	299 (68.6%)	85 (70.2%)	P=0.408
Mean size mm, (sd)	31.3 (13.9)	29.5 (11.3)	37.9 (19.4)	p<0.001
Location n, (%)				
Right sided	174 (31.2%)	117 (67.2%)	57 (32.8%)	p<0.001
Left sided	383 (68.8%)	319 (83.3%)	64 (16.7%)	
Histology n, (%)				
Tubular adenoma	138 (24.7%)	112 (25.7%)	26 (21.5%)	p=0.305
Tubulovillous adenoma	319 (57.3%)	245 (56.1%)	74 (61.1%)	
Villous adenoma	53 (9.5%)	40 (9.1%)	13 (10.7%)	
Serrated polyp	9 (1.6%)	6 (1.4%)	3 (2.5%)	
Metaplastic	15 (2.7%)	15 (3.4%)	0	
Inflammatory	1 (0.2%)	1 (0.2%)	0	
Unknown	22 (3.9%)	17 (3.9%)	5 (4.1%)	
Dysplastic grade n, (%)				
Non-dysplastic	16 (2.9%)	16 (3.7%)	0	p=0.483
Low grade dysplasia	360 (64.6%)	283 (64.9%)	77 (63.4%)	
High grade dysplasia	164 (29.4%)	123 (28.2%)	41 (33.8%)	
Not known	17 (3.1%)	14 (3.2%)	3 (2.5%)	

Table 36- Characteristics of patients and lesions classified by initial therapeutic modality

Outcomes in endoscopically managed LSCP

436/557 (78.3%) LSCP were managed endoscopically in the first instance. Outcomes in this group are shown in table 37.

Outcome	Number , % (n=436)
Successful resection (no recurrence at 3-12 months)	340 (78.0%)
Residual or recurrent polyp at 12 months	26 (6.0%)
Surgery for histologically confirmed cancer in LCSP	19 (4.4%)
Surgery for failed endoscopic therapy in LSCP assessed as benign	51 (11.7%)

Table 37- Outcome following endoscopic management of LSCP

29/436 (6.7%) LSCP initially managed endoscopically were subsequently found to contain malignancy. This was detected in the endoscopic resection specimen in 21 cases and in the surgical resection specimen in 8 cases. In 19 of 21 (90.5%) cancers detected in the endoscopic resection specimen, subsequent surgery was performed. The remaining two cases were managed conservatively as endoscopic excision was complete histologically.

Recurrent or residual polyp (RRP) was detected in 71/436 (16.3%) patients at 3 month surveillance and 26/436 (6.0%) patients at 12 months. 18/26 patients underwent both 3 month and 12 month surveillance. RRP was present in 5/18 (27.8%) patients at 12 months where no RRP had been detected at 3 months

70/436 (16.1%) lesions initially managed endoscopically subsequently required surgery (table 36). The indication for surgery was the presence of malignancy in the endoscopic resection specimen in 19/70. In the remaining 51 cases, the lesion was not amenable to further endoscopic management, necessitating surgery to completely excise the lesion. Within this group, the stated reasons were: Technical limitations to endoscopic management (such as involvement of the ileo-caecal valve, size, difficult access or previous attempts at resection)

in 38/51 and recurrence or residual polyp which was not manageable endoscopically in 7/51. The reason was not given in 6/51 cases.

In univariable analyses, none of the following variables were associated with incidence of RRP at 12 months, subsequent need for surgery or presence of malignancy in the resection specimen: age and gender of the patient, histological type or grade of the LSCP, site of the LSCP or technique of removal (piecemeal or en-bloc). Only increasing size was shown to be associated with these outcomes (table 38). Compared to lesions less than 30 mm in size, a lesion 30 to 39mm in size had a relative risk of being malignant of 3.2 (95% CI 1.4-7.4) and of 4.1 (2.3-7.3) for subsequently needing surgery. A lesion 40 mm or larger in size had a relative risk of being malignant compared to lesions less than 40mm of 3.7 (1.7-8.2) and of 2.7 (1.5-4.7) for subsequently requiring surgery (table 39)

Outcome	Number in which cancer subsequently detected, %
Primary Surgical management of LSCP	25/121 (20.6%)
Endoscopic resection of LSCP	21/436 (4.8%)
Secondary surgical management of LSCP following initial endoscopic management	8/51 (15.7%)

Table 38- Cancer detection in resection specimens

Size of LSCP	Residual or recurrent polyp at 12 months	p	Rate of malignancy in LSCP	p	Subsequent need for surgery	p	Mean number of endoscopic procedures	p
20-29mm (n=232)	12 (5.2%)	0.686	8 (3.4%)	0.020	18 (7.8%)	<0.001	1.84	<0.001
30-39mm (n=113)	7 (6.2%)		8 (7.1%)		27 (23.9%)		2.31	
≥ 40mm (n=91)	7 (7.7%)		13 (14.3%)		25 (27.5%)		2.33	

Table 39- Association of size of LSCP with outcome of endoscopic management, presence of malignancy, need for surgery and number of endoscopic procedures

Surgical Management

Surgery was the initial therapeutic modality for 121/557 (21.7%) LSCPs. All these lesions had been assessed, clinically or histologically, as benign. 55/121 (45.6%) were not amenable to endoscopic management for the following reasons: 4 (6.6%) involved the ileocaecal valve; 9 (14.8%) abutted the dentate line; 42 (68.9%) were too large for endoscopic removal (the mean size of LCSP in this subgroup was 43.8mm). The indication for surgery was not recorded in 66 (54.5%) cases. Despite no pre-surgical evidence of malignancy, cancer was present in the surgical resection specimen of 25/121 (20.7%) lesions. There was a non-significant positive trend between increasing size of lesions managed surgically and cancer in the resection specimen: 5/36 (13.9%) of lesions 20-29mm in size, 8/35 (22.9%) 30-39mm in size and 12/50 (24.0%) ≥40mm in size were malignant (p=0.484).

Adverse events

In the group of patients managed endoscopically initially, 18/436 (4.1%) patients required admission following the procedure: 13 due to bleeding (11 managed conservatively, 2 required endoscopy, none required surgery), three were due to pain and two due to perforations. Of the two perforations, one was managed conservatively and one required surgery. No deaths as a result of endoscopic management of lesions were recorded.

Screening centres were asked to report surgical complications and whether patients were alive 30 days following the surgical procedure in the surgically managed group. Data were returned for 108/121 (92.6%) of patients. 1/121 (0.83%) died 4 days following a surgical procedure due to myocardial infarction following a postoperative diverticular bleed. 12/121 (9.9%) surgical complications in this group were reported: 2 anastamotic complications, 6 wound infections, 1 post-surgical bleed, 3 postoperative ileus and one intra-abdominal sepsis were reported.

Adverse events were more frequent in the surgically managed group compared to the endoscopic group (13/121 vs. 18/436, $p=0.011$). The difference in deaths in each group (1/121 vs. 0/436) was not significant ($p=0.217$)

The mean length of stay in patients undergoing surgery was 7.0 days (range 1-27 days).

Variation between screening centres

Rates of surgery as the primary management for LSCP were analysed at 8 centres which had managed 20 or more LSCP (table 40). Only one centre had a primary surgical rate out-with the 80% confidence interval for the population. This may be explained by the centre also having a mean size of LSCP out-with the 95% confidence interval for the population.

Screening Centre	Number of LSCP	Mean size[#]	Primary surgical management (n)	Proportion managed surgically (%)	Lower 80% CI for proportion managed surgically (%)[*]
1	21	29.3	6	28.6	15.9
2	74	30.4	8	10.8	6.2
3	37	28.1	8	21.6	12.9
4	27	34.1	2	7.4	0.9
5	20	28.8	7	35.0	21.3
6	24	28.0	5	20.8	10.2
7	33	32.2	5	15.2	7.1
8	28	38.6	10	35.7	24.1

Table 40- Proportion of LSCP initially managed surgically at 8 screening centres with 20 or more LSCP

4.2.4- Discussion

This study demonstrates that endoscopic management of large sessile colonic polyps (LSCP) in the NHS Bowel Cancer Screening Programme is safe, effective and avoids the need for surgery in the majority of cases. This nationwide study is the largest series of LSCP management from Europe or the USA and demonstrates clinical outcomes that compare favourably with existing reports (table 40).

	BCSP 2011	Moss 2011	Ferrara 2010	Khashab 2009	Arebi 2007
Number	436	479	182	136	161
Mean size	29.5mm	35.6mm	24.7mm	32.8mm	32.5mm
Need for surgery	16.1%	16.3%	8.3%	0	4.3%
Cancer in resection specimen	6.7%	6.9%	7.3%	0.7%	5.5%
12 month recurrence	6.0%	20.4%	6.9%	17.6%	40%
Adverse events	4.1% admission 3.0% bleed 0.5% perforation	7.7% admission 2.9% bleeding 1.3% perforation	All admitted for 24-72 hours 12.4% bleeding 2.2% PPS 1.1% perforation	4.5% bleeding 0 perforation	5.7% bleeding 0 perforation

Table 41- Comparison with other published series of large sessile colonic polyps

Endoscopic management of LSCP in this study was associated with fewer adverse events than surgical management. The post-polypectomy bleeding rate of 3.0% is similar to other series which report rates of 2.9% - 5.7% (Swan et al 2009; Moss et al 2011; Ferrara et al 2010; Khashab et al 2009; Arebi et al 2007). This is despite aspirin not being stopped routinely in keeping with current anticoagulation management guidelines (Veitch et al 2008). Site and size of the LSCP appears to be important in determining the initial therapeutic modality with larger and right sided lesions more likely to be managed surgically. This would suggest that the expertise of the endoscopist and their previous experience has an effect on the initial treatment decision. This is reflected in the centre to centre variation of the proportion of LSCPs managed surgically or endoscopically. Availability and extent of local expertise influence treatment decisions.

Rectal LSCPs were analysed as a subgroup to explore the variation in practice between centres in more detail. 205 rectal LSCPs were identified (mean size 33.0mm). 17 were managed with TEMS in the first instance (mean size 28.5mm, $p=0.42$ compared to mean size of all rectal LSCPs). Lesions managed by TEMS tended to be smaller than other rectal lesions managed with alternative surgical approaches ($n=24$, mean size 46.0 mm, $p=0.02$). Eleven lesions were managed by TEMS after an initial attempt at EMR, these tended to be larger lesions (mean size 39.7 mm, $p=0.16$ compared to other surgically managed rectal lesions). There was no clustering around particular centres in terms of proportion of rectal lesions managed by TEMS. Due to the limited data available it was not possible to fully evaluate what factors influence whether TEMS was used for rectal LSCPs. Local availability is likely to be an important factor. The distance of the LSCP from the anal verge was not recorded so this important variable could not be accounted for.

Subsequent need for surgery following initial endoscopic therapy is associated with increasing size of the lesion. Polyps 40 mm or greater in size are associated with a 27% need for surgery following initial endoscopic management, 7.7% rate of residual or recurrent polyp at 12 months, and a 14% risk of the LSCP being malignant. The management of these lesions should be carefully considered and prompt referral for management at specialist centres may be appropriate.

Recurrence or presence of residual polyp (RRP) at 12 months is a recognised outcome measure for LSCP, however, there is considerable heterogeneity in how this outcome is reported (Swan et al 2009; Moss et al 2011; Ferrara et al 2010; Khashab et al 2009; Arebi et al 2007). In the present study, RRP at 12 months occurred in 6.0% of endoscopically managed lesions. This is in keeping with other series of endoscopically managed large colonic polyps (table 40). Late recurrence of lesions (no RRP at 3 months but RRP detected at 12 months) occurred fairly frequently (5/18 (27.8%). This may be due to regrowth of adenoma from an endoscopically undetectable sub-surface dysplastic focus, from a small focus of endoscopically visible but undetected residual adenoma, or due to mis-identification of the original polypectomy site. Khashab et al (2009) report a considerably lower rate of late recurrence following routine biopsy of the polypectomy scar at 12 months.¹⁴ They studied 136 large polyps (≥ 2 cm) removed by EMR. 24 (17.6%) had macroscopic evidence of recurrence at follow up. 18 displayed recurrence at first follow up whilst 6 (4.4%)

demonstrated ‘late recurrence’ – the presence of recurrence despite initially normal surveillance. Negative biopsy of the polypectomy scar was associated with lower recurrence rates in long term follow up. 92 of 94 (97.9%) of normal appearing scars with negative scar biopsies remained free from recurrence at one year. 6 of 42 (85.7%, $p=0.005$) polyps with macroscopic or microscopic evidence of recurrence were successfully eradicated at long term follow up. In our study, it is not known if polypectomy scars were routinely biopsied in cases undergoing 3 month endoscopy review. We recommend that, following endoscopic resection of LSCP in the BCSP, surveillance of the polypectomy site is conducted both at 3 months and at 12 months in keeping with existing guidelines and that the polypectomy site is routinely photographed (or videoed) and biopsied (Atkin et al 2002). Site identification should be assisted by placing an endoscopic tattoo at the time of the initial procedure.

A recent multicentre Australian study of EMR for large sessile colonic polyps produced similar results to those seen in our study (table 40) (Moss et al 2011). In their study of 479 LSCP (mean size 35.6mm), 464 lesions were managed with EMR. Risk factors for failure of endoscopic therapy were lesions in a difficult position for EMR, involvement of the ileocaecal valve, and a previous attempt by the referring endoscopist. A higher proportion of LSCP were managed surgically in the first instance in our study. This reflects the observational nature of our study which encompasses broad practice within a national screening programme. The Australian study was only of lesions referred to a specialist group of colonoscopists with an interest in advanced polypectomy, thus, no data on lesions not referred into the service are presented. Two notable comparisons can be made. First, the clinical outcomes in the endoscopically managed groups of the two studies are similar. The mean size of LSCP in our study was smaller than in the Australian study (31.3mm vs. 35.6mm, $p<0.001$), however, this suggests endoscopic resection of LSCP can be delivered by a large national Bowel Cancer Screening Programme at a standard comparable to international experience and small groups of experts. It is important to note that all screening colonoscopists within the BCSP have passed a detailed screening accreditation exam, comprising multiple choice exam, audit of previous 12 months’ practice and assessment of colonoscopy technique over 2 colonoscopies by 2 screening examiners. At the time of this study, polypectomy technique was not assessed as part of this process. Second, the bleeding rates in the two studies are similar. In Australia it has been routine practice to stop aspirin prior to polypectomy (Gastrointestinal Expert Group 2011). This is not the case in England

where low dose aspirin is usually continued irrespective of therapy to minimise the risks associated with cessation of antiplatelet therapy (Veitch et al 2008). This is indirect evidence to support the continuation of low dose aspirin during polypectomy, even for large sessile lesions.

A previous study by the same Australian group has suggested a potential cost saving of endoscopic therapy compared to surgical management of US\$6990 per patient (Swan et al 2009). Although we have not conducted health economic analysis of our data, it is likely that endoscopic management in the country is also associated with a significant cost saving over surgery.

Our study has a number of limitations. Firstly, it was a retrospective observational study which introduces the possibility of selection bias. By obtaining data on all LSCP encountered in the BCSP from the national database we hoped to minimise this, however, the second phase of the data collection process, which involved further data collection from the screening centre may have been susceptible to selection bias. However, given the size and wide coverage of this study we do not think it would affect our conclusions.

Second, we were not able to collect more detailed information on the endoscopic technique employed for resection of the LSCP. This included details of the endoscopic assessment (Paris classification, Kudo pit pattern, use of adjuncts to white light endoscopy such as narrow band imaging, ease of access to the polyp), and details of the polypectomy itself (EMR technique, type of injection solution used, diathermy settings, need for argon plasma coagulation). We have recommended that these data are routinely collected for all LSCP resections in the NHS Bowel Cancer Screening Programme for quality assurance and service development purposes. An additional consideration we have not been able to examine is the patient experience of the different therapeutic modalities. A study of patient acceptability and impact on quality of life of surgical vs. endoscopic management of LSCP would be desirable.

In summary, endoscopic management of LSCPs is effective and provides advantages over surgical management in terms of safety and cost.

There is now a substantial evidence base supporting endoscopic management of LSCP as the preferred choice of initial therapy. Endoscopic therapy should only be attempted by colonoscopists competent in advanced polypectomy techniques such as EMR and comfortable with the endoscopic management of complications. Each lesion should be

extremely carefully assessed for evidence of malignancy prior to attempted resection. This may necessitate the use of techniques such as narrow-band imaging, assessing lift characteristics and chromendoscopy. Where there is a high suspicion that a lesion may be malignant, oncological principles should be followed and a surgical or endoscopic en-bloc resection technique should be used.

Certain features of an LCSP predict failure of endoscopic therapy, recurrence and need for surgery. These features include size greater than 30-40mm, right sided location, involvement of the ileocaecal valve, difficult endoscopic access and previous attempts at resection. A low threshold should exist for early referral of lesions displaying such features to an expert endoscopist. Consideration should be given to the creation of a network of expert colonoscopists to optimise clinical outcomes in difficult cases.

5.0- Discussion

5.1.0- Detection of Neoplasia in the NHS Bowel Cancer Screening Programme

5.1.1- Use of adenoma detection rather than cancer detection as a measure of colonoscopic performance

The aim of Chapter 1 was to examine measures of performance of colonoscopy in the NHS Bowel Cancer Screening Programme (BCSP), the main aim of colonoscopy being neoplasia detection.

Neoplasia, as a term, describes any lesion arising due to ‘abnormal or uncontrolled growth of cells’. Neoplasia therefore, is an umbrella term that encompasses a range of lesions reflecting the adenoma carcinoma sequence (Vogelstein 1988), from small tubular adenomas displaying low grade dysplasia to Dukes stage D metastatic colorectal cancer. The clinical significance of lesions at the earlier end of this spectrum is less clearly defined than at the advanced end. The main aim of the BCSP is to detect lesions that are about to or have already become malignant but are pre-symptomatic and at a curable stage. Paradoxically, measuring the detection of this group of lesions is not ideal because cancers or advanced neoplastic lesions (adenomas ≥ 10 mm in size or displaying high grade dysplasia) are detected relatively infrequently (at around 20 to 30% of BCSP colonoscopies) compared to all adenomas (one or more adenomas are detected in around 50% of procedures). When assessing the performance of individual colonoscopists, the relative infrequency of advanced lesions and in particular, cancer, means the confidence intervals around detection rates are wide, limiting the usefulness of measures such as cancer detection rate or advanced adenoma detection rate. Adenoma detection rate (ADR) tends to have narrower confidence intervals, implying that a single point estimate of an individual colonoscopist’s ADR is more reliable than a measure of a less frequently occurring lesion for a given number of procedures.

Work described in Chapter 1.2 demonstrates a ‘ceiling effect’ for colonoscopy withdrawal time on adenoma detection rate. Due to the finite number of detectable adenomas in a colon, longer withdrawal time and adenoma detection do not have a positive linear association *ad infinitum*. Rather, there is a limit at which increasing withdrawal time is no longer associated with increasing adenoma detection. In the BCSP, no such relationship is demonstrated for advanced adenoma. Increasing withdrawal time is not associated with increasing detection of

such lesions. This is likely to be because the ‘ceiling’ for detection of large lesions (over 90% of advanced adenomas are 10mm or greater in size) is below the mean withdrawal time for the majority of BCSP colonoscopists (the mean negative complete colonoscopy withdrawal time CWT (nc-CWT) was 9.4 minutes, the lowest mean nc-CWT was 5.4 minutes).

An important function of a measure of colonoscopic performance is to differentiate ‘good’ from ‘bad’. It has been shown that ADR correlates with nc-CWT. High ADR and longer nc-CWT are generally thought of as traits of a good colonoscopist (Milan 2008). Advanced adenoma detection rate does not correlate with caecal intubation rate (one can extrapolate that cancer detection rate would not correlate with ADR either) and is therefore not as useful as ADR in assessing the quality of colonoscopy in the BCSP setting. Advanced adenoma detection rate does not reflect the same range of performance as adenoma detection rate.

A measure of colonoscopic performance should depend on technical factors pertaining to the detection of the lesion rather than the underlying prevalence of the lesion itself. Cancer incidence rates are known to vary from region to region in England (50 per 100,000 men in London compared to 65 per 100,000 men in the North-East, a 30% relative difference) (Cancer Research UK 2010). Data from the pilot study of the CRC screening in the UK showed a reduction in cancer detection rates in subsequent screening rounds, no such variation in adenoma detection rate was demonstrated in either the pilot or the current BCSP (Chapter 3.1.3). Epidemiological data on adenoma incidence in different regions of England is scarce. It is reasonable to state however, that cancer detection rate is more dependent on the underlying prevalence in the group undergoing colonoscopy than adenoma detection rate.

5.1.2- Why are small colonic adenomas important?

The clinical significance of small colonic adenomas has been questioned. As few as 1% of small adenomas may progress to cancer. This risk is higher for advanced adenomas (Brenner 2007), which progress to malignancy at a rate of around 5% per year. The direct clinical benefit of removing a single small adenoma is therefore small. The importance of detecting and removing small lesions is justified by three main arguments:

1. Firstly, detection of small adenomas is a marker of completeness of mucosal inspection which is the key objective of colonoscopy. Kaminski (2010) demonstrated that colonoscopists with lower adenoma detection rates were more likely to have missed a

cancer (which was subsequently diagnosed as an interval cancer) than colonoscopists with higher adenoma detection rates. This argument is countered by the risk of adverse events incurred by polypectomy. However, the majority of complications arise from polypectomy on advanced lesions. Removal of small lesions is generally safe (Heldwein 2005).

2. Secondly, studies which have demonstrated a reduction in CRC incidence (Winawer 1993) and mortality (Mandel 1993; Hardcastle 1996; Kronborg 1996) have all relied on removal of all detected adenomas. Within the screening setting therefore, detection and removal of all adenomas is presently viewed as being mandatory.
3. Thirdly, the presence of small adenomas is a marker of future risk of advanced neoplasia being detected in an individual. Many studies have quantified this risk (Martinez 2001 (pooled analysis), Saini 2006 (meta-analysis)). An individual's future risk of advanced neoplasia increases 2.5 fold if three or more small adenomas are detected (Saini 2006). Colonoscopic surveillance may be directed at these individuals. Conversely, if an individual has had a thorough colonoscopy and only found to have 0, 1 or 2 small adenomas, their future risk may be lower than that of the general population.
4. It is not possible at present to detect which small adenomas will progress to become large adenomas or cancer. We assume therefore, that all small lesions have the same future risk of progression.

Outside the screening setting, the context of the colonoscopy must be taken into account. Clearly, an elderly patient with multiple comorbidities is unlikely to benefit from the detection and removal of small colonic polyps in terms of assessing or reducing their CRC risk. However, even in this group, adenoma detection remains a marker of completeness of examination

5.1.3- Efficacy of colonoscopy in the NHS Bowel Cancer Screening Programme

In Chapter 1, adenoma detection rate and other colonoscopy performance indicators are shown for the BCSP. Whilst the emphasis of the chapter is on performance indicators, an important product of this work was an assessment of the efficacy of colonoscopy within the BCSP. This work contributed to the quality assurance processes of the screening programme itself. The initial work of selecting appropriate performance indicators and defining how they

should be calculated has formed the basis of how colonoscopy performance indicators are produced in the BCSP.

The efficacy of colonoscopy in the BCSP compares favourably to performance described in other studies of large scale screening colonoscopy (Kaminski 2010) and to previous reports of colonoscopy practice in the UK (Bowles 2004; Weller 2006). However, as in previous reports of colonoscopic performance (Atkin 2004, Harewood 2005), a wide variation in measures such as ADR, withdrawal time and intubation rate was shown.

The original hypothesis of this chapter was ‘adenoma detection rate is not correlated with other measures of colonoscopic performance in the BCSP.’ The data presented in Chapter 1 refute the null hypothesis. ADR has been shown to correlate with withdrawal time, intubation rate, rectal retroversion rate and polyp retrieval rate. This reinforces the position of ADR as the key indicator of colonoscopy performance. However, data presented in Chapter 1 show that additional consideration must be made of the population in which ADR is calculated prior to comparing ADR. Variation in age and gender between populations may account for important differences in ADR, requiring standardisation to allow reliable comparisons to be made.

5.2.0- Management of Neoplasia in the NHS Bowel Cancer Screening Programme

Chapter 2.1 explores outcomes at 12 month surveillance colonoscopy in patients with high risk adenomas at baseline screening colonoscopy. The headline finding was a yield at surveillance colonoscopy of 0.9% for colorectal cancer and 5.7% for one or more advanced adenomas. This is a notable finding as it justifies the role of early surveillance colonoscopy in this group of patients despite initial high quality screening colonoscopy. Patient factors, including age and gender were shown not to be associated with outcome at 12 months. Baseline polyp characteristics, including right sided location and presence of villous histology, were shown to be associated with the presence of advanced colonic neoplasia at 12 months. These findings may help to refine surveillance criteria in the future.

It is important to reflect on why so many lesions were detected at 12 months despite a high quality screening colonoscopy. It can be assumed that the majority of advanced lesions detected at 12 months must have been missed at baseline colonoscopy. Indeed, the rate of such lesions in this study was similar to previous reports of missed lesions 10mm or greater in size (Rex 1997; van Rijn 2007). However, this polyp rich population may also be susceptible to accumulation of new adenomas and it is difficult to quantify the contribution of recurrent lesions at sites of incomplete resection.

In chapter 2.2 the management of large sessile colonic polyps (LSCP) in the BCSP was investigated. This was the largest study of polypectomy practice performed in England. In order to gather enough detailed data about the management of each LSCP, additional data had to be gathered from local screening centres to supplement the data in the national database. This was a large project which required the assistance of many screening practitioners around the country. Due to the size of the study and the level of detail needed, the data collection period took longer than planned but provided a comprehensive dataset on the management of over 550 polyps. Due to the retrospective observational nature of the study and the diversity in management of the lesions, rationalising the data was challenging but the use of clearly defined outcome measures, derived from the existing literature, facilitated this.

Size and location of the LSCP were shown to be clear determinants of the initial treatment modality. Increasing size was also shown to be associated with failure of endoscopic therapy, subsequent need for surgery and presence of malignancy in the resection specimen. Endoscopic management was shown to be as safe and effective as other comparable published series. Endoscopy had a lower adverse event profile compared to surgery. There was a clear variation in the proportion of lesion managed surgically or endoscopically between screening centres that could not be accounted for by size of the lesions. It is likely that availability of local expertise is an important factor.

This study has a number of important implications. Firstly, the high failure rates of endoscopic management seen in larger LSCP, particularly those over 40mm in size, suggests that management decisions in this group should be carefully considered and possibly referred to a clinician with experience in their management.

Higher rates of delayed recurrence were seen in this study compared to rates suggested in the literature. This may, in part, be due to the retrospective nature of the study. It seems reasonable to suggest that colonoscopists should routinely biopsy polypectomy scars at three month check colonoscopy to minimise the risk of missing residual or recurrent adenoma. However, the data collected for this study does not answer the question of whether this would reduce the rate of endoscopic failure or need for surgery.

5.3.0- Improving data quality in the BCSP database

During the process of generating data for chapter 1 of this thesis and subsequently producing a report on colonoscopy quality indicators in the NHS Bowel Cancer Screening Programme, a number of data quality issues within the BCSP national database were raised.

Dissemination of these issues within these screening programmes could help to improve the quality of future data collection and analysis. Data quality is critical to the validity of any analysis. Specific areas of concern regard missing data, implausible data, duplicate data and digit preferences. The overall quality of the data however is of a reasonable standard and adequate to allow further statistical analysis.

The following recommendations to the BCSP Evaluation Group were made to improve the general quality of data in the BCSS national database:

1. **Flags incorporated into BCSS software to alert users that an unexpected value has been entered.**

Table 42 below demonstrates suggested limits for the expected range.

If data entered is outside the expected range, a warning should appear stating `The figure you have entered is outside the expected range for this field. Please check and re-enter`. Following re-entry of the item of data, no warning would appear. This would give those entering the data the opportunity to double check extreme values. A second method, which would be much simpler to quickly implement is to simply restrict the range of possible values that can be entered by using a 'plausible range' i.e. outside this range values are considered implausible.

Data field	Expected range	Plausible range
Colonoscopy withdrawal time	5-20 minutes	0-120 minutes
Midazolam dose	1-5mg	0-50mg
Fentanyl dose	12-100 mcg	0-500 mcg
Pethidine dose	12-100 mg	0-500 mg
Buscopan dose	10-40 mg	0-100mg
Height	1.5-2.0 m	1.0-2.5 m
Weight	50-100kg	20-300 kg
Number of cigarettes per day	0-40	0-150
Alcohol quantity per week	0-40 units	0-400

Table 42- Recommended ranges for specific datafields in the BCSS

2. Colonoscopists are given unique identifier codes.

In the original BCSS database, individual colonoscopists could have more than one code if they performed colonoscopy at more than one site. This complicated data analysis and made calculation of colonoscopist level performance indicators prone to error. Assigning a unique identifier to each colonoscopist would avoid this.

3. Entonox use

This field should be a yes/no option rather than requiring a dose. This reflects the way this drug is administered.

4. Standardisation of method for recording timing of colonoscopy

It was apparent that there was terminal digit preference within the colonoscopy withdrawal time dataset. This was demonstrated by the clustering of values at 5, 10 and 15 minutes. Informal discussions with screening practitioners revealed a number of different methods were used to record withdrawal time. As a result of these findings a recommendation was made to the BCSP evaluation group to recommend that screening practitioners should use a standardised method for recording withdrawal time. Recording should commence when colonoscopic evaluation of the caecal pole (as identified by anatomical landmarks) commences. Withdrawal time should not include time spent attempting to enter the ileocaecal valve. Recording should stop when the colonoscope is removed through the anus. Withdrawal time should be rounded to the nearest minute.

5. Recording of adverse events

Comparison of data on adverse events in the BCSS with data obtained from screening centres showed that adverse events were infrequently recorded on the BCSS. In addition, where an event was recorded, insufficient data to characterise the event or stratify its severity was present. In light of this, screening centres were reminded of the need to record all adverse events on the BCSS and it was recommended that a

minimum dataset for adverse events be introduced to allow stratification according to the BCSP adverse event stratification tool (Chilton 2010).

5.4.0- Can adenoma detection rate be improved upon as a measure of colonoscopic quality?

An inherent limitation of ADR is that it does not account for multiple adenomas. 49% of all adenomas in the cohort of patients described in section 3.1 were present in addition to the index adenoma. Measures of total numbers of adenomas have not previously been widely used. The work in this thesis has contributed to the description and validation of two novel measures (mean adenomas per procedure (MAP) mean adenomas per positive procedure (MAP+)). Both these measures are now routinely reported by the BCSP. Because they are more aligned with the ethos of screening colonoscopy as previously described, it is envisaged that they will become more widely used by the screening community, and potentially in the non screening setting. These measures offer an added insight into colonoscopist performance. Figure 14 in chapter 1.1 demonstrated clusters of colonoscopists defined by their ADR and MAP. It can be inferred that there is a difference between the two groups of colonoscopists, both with good ADR but one with MAP around 1.8 and the other with higher MAP. The second group are able to detect not only adenomas in a lot of patients (high ADR) but also multiple adenomas in those patients (high MAP). Some colonoscopists are capable of attaining MAP values around 3.0 which must reflect attention to use of manoeuvres to maximise adenoma detection rate or other non-technical skills. This group of colonoscopists have become colloquially known as ‘superdetectors’. Further investigation into their colonoscopy performance based on known technical performance indicators and potentially their non-technical skills may be useful to identify attributes of best practice.

These measures of total adenoma detection are not novel. Barclay et al (2006), in their important study which confirmed the correlation between ADR and withdrawal time used a measure of total adenoma detection. MAP and MAP+ however, are more difficult to measure, requiring greater detail of recording than ADR. This is particularly hard to achieve in routine colonoscopy practice (outside the screening programme) and illustrates one of the strengths of the BCSP in terms of the comprehensiveness of data captured for each colonoscopy.

5.5.0- How will the addition of Flexible Sigmoidoscopy impact upon measures of colonoscopy performance?

The UK flexible sigmoidoscopy trial (Atkin et al 2010) randomised 170,432 individuals to an intervention group (flexible sigmoidoscopy at between 55 and 64 years of age) or a control group (which were simply observed). 40,764 individuals underwent flexible sigmoidoscopy. Colonoscopy was recommended if any of the following were found: an adenoma 1 cm or larger in size; three or more adenomas; tubulovillous or villous histology; severe dysplasia or malignant disease or 20 or more hyperplastic polyps above the distal rectum. 5% of individuals met one or more of these criteria at sigmoidoscopy and were recommended colonoscopy. Median follow up extended to 11.2 years. Colorectal cancer incidence in the intervention group was reduced by 23% in intention to treat analysis (hazard ratio 0.77, 95% CI 0.70-0.84). Mortality was reduced by 31% (hazard ratio 0.69, 95% CI 0.59-0.82). No reduction in mortality from proximal cancers was seen suggesting the protection against dying from colorectal cancer conferred by flexible sigmoidoscopy is confined to the distal colon. Three other trials of flexible sigmoidoscopy screening (Segnan N et al 2002; Weissfield J et al 2005; Hoff et al 2009) have reported initial results or are nearing completion; none have shown the same degree of benefit as the UK trial, probably due to variations in the study protocols.

On the basis of the evidence from the flexible sigmoidoscopy trials and a re-appraisal of the clinical and economic impact of screening options (Whyte et al 2011), the addition of a once-only flexible sigmoidoscopy between the ages of 55-59 years is to be added to the current NHS screening strategy. FOBt will continue from 60-74 years.

This change in screening strategy will necessitate a range of performance indicators for screening colonoscopy to be defined. They will reflect those currently used for colonoscopy in terms of incorporating technical measures, safety measures and measures of acceptability. Some measure of depth of insertion will be required. This is less easy to define than caecal intubation rate as there is no definitive landmark, the use of technologies such as magnetic Scopeguide (Olympus, Japan) imaging systems may facilitate this (Painter et al 1999).

In the longer term, flexible sigmoidoscopy prior to FOB testing is likely to change the positivity rate of FOB testing and potentially the yield of colonoscopy in those with a positive

FOB test. Minimum standards and targets for pathology based measure of colonoscopy performance such as ADR and MAP may have to be modified as a result.

5.6.0- How will the advent of optical diagnosis impact on technical measures of colonoscopy?

Current practice in colonoscopy necessitates the detection and removal of all adenomas. This practice creates a large workload for pathology services which are required to analyse each resected adenoma. In addition, each polypectomy exposes the patient to the small risk of a complication occurring.

New technologies such as Narrow Band Imaging (NBI) allow more detailed characterisation of colonic lesion than conventional white light endoscopy. NBI (Olympus, Japan) is an optical imaging modality which enhances mucosal detail and vascular structures by using a short wavelength, narrow-bandwidth blue light. It has been shown to be more effective than white light endoscopy in differentiating neoplastic from non neoplastic lesions (East 2007c, East 2008b; van de Broek 2008).

The DISCARD study (Ignatovic et al 2010) was a prospective cohort study comparing optical diagnosis with histology. The authors state that ‘the capability to correctly diagnose a polyp during colonoscopy (optical diagnosis) would allow recto-sigmoid hyperplastic polyps to be left in situ and small adenomas to be resected and discarded without a need for formal histopathology, possibly leading to substantial savings in time and cost, and reduction in patient risk’. The study demonstrated a sensitivity of 0.94 (95% CI 0.90–0.97) and specificity 0.89 (0.78–0.95) for adenomas with an overall accuracy of 0.93 (95% CI 0.89–0.96) for polyp characterisation. The study was limited by being a single centre study performed by expert colonoscopists. A further study (DISCARD 2) is planned with the objective of assessing optical diagnosis in a multicentre trial.

It is likely that in the future, optical diagnosis for lesions less than 10mm in size will become standard practice. Further evidence of the efficacy of optical diagnosis in the screening setting would be required. The concern would remain that high grade dysplasia or cancer

could be missed in a sub-centimetre lesion by discarding it rather than sending it for histology. Reassuringly, in a study of polyp cancers in the BCSP, only 103 of 34,959 polyps (0.29%) less than 10mm in size were polyp cancers (Lee et al 2010).

Measures of colonoscopy performance which reflect lesion detection (such as ADR and MAP) depend on histological confirmation of the lesion to calculate the 'numerator'. If optical diagnosis were to change, the method of calculating ADR would need to be adapted.

One option would be to remove the need for histological confirmation of the lesion and calculate a polyp detection rate (PDR), whereby the numerator consists of all lesions detected, regardless of their nature. Using data from colonoscopists in the BCSP, ADR and PDR can be shown to have good positive correlation ($r=0.83$, $p<0.001$) as shown in figure 21.

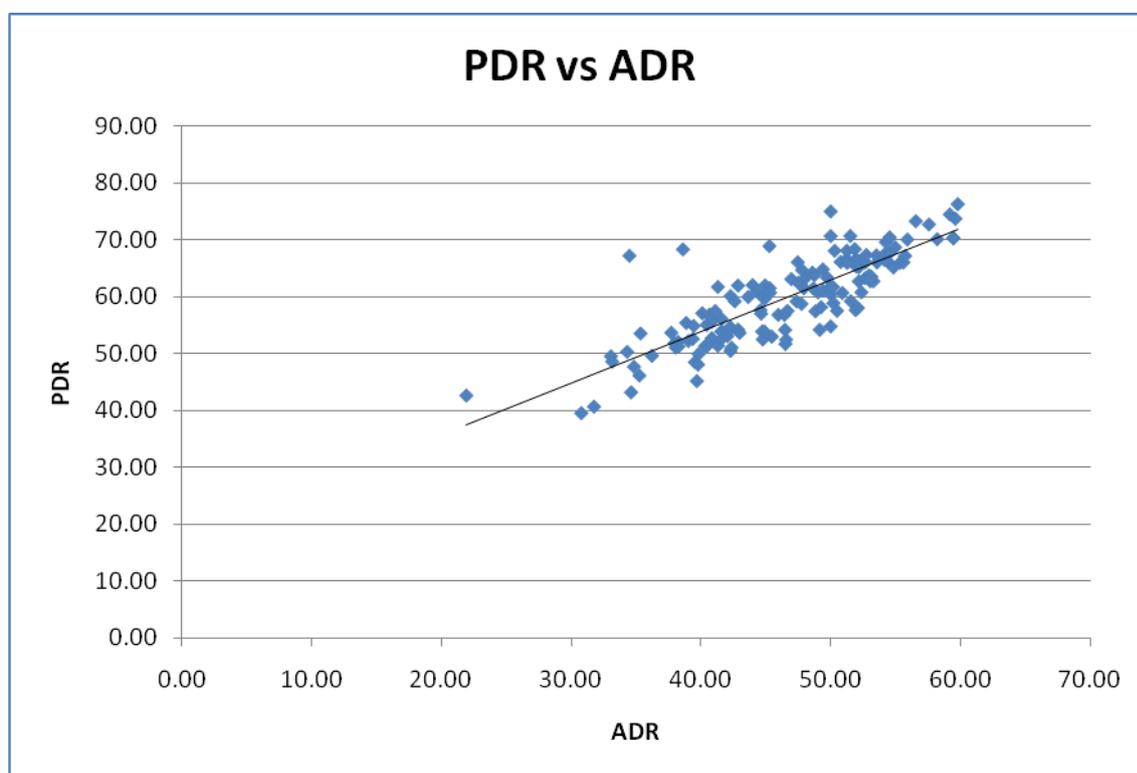


Figure 21- Correlation of PDR and ADR for colonoscopists in the BCSP

Francis et al (2011) have suggested that PDR can be accurately converted to ADR using a conversion factor (adenoma:polyp detection rate quotient- APDRQ). For the BCSP population in Figure 21 the APDRQ would be 0.778. The limitation of PDR is that it can be inflated by colonoscopists who remove a lot of non-neoplastic polyps or even biopsy normal

tissue. This weakness could be attenuated by regular monitoring or audit of colonoscopists' practice.

If optical diagnosis for lesions less than 10mm in size, measures of adenoma detection and total adenoma detection would need to rely on photographic or video confirmation of the lesion being an adenoma to remain accurate. Similar adjustments would need to be made immunohistochemical FOB testing (iFOBT) was introduced.

5.7.0- Use of colonoscopy performance indicators as quality indicators

The evolution of much of this thesis has been driven in part by the requirement for the data being generated to be used not just for research but also to inform quality assurance of colonoscopy in the BCSP. The data has been used to identify poor performance by using 80% confidence intervals around adenoma detection rates to identify outliers against a predefined target. The work in Chapter One also contributed towards the development of quality assurance guidelines for colonoscopy in the BCSP (Chilton 2011). This process is illustrated using a funnel plot (figure 22). 80% confidence intervals are used for quality assurance (rather than 95% confidence intervals) because the purpose of the confidence is to detect outlying performance rather than certainty about the measure. An 80% confidence limit means you can be 80% sure that the true underlying value of the measure is between the given limits. 80% confidence limits are used here because pro-active quality assurance should not require the same degree of certainty as for example a randomised controlled trial of two drugs. The 95% confidence limits are stricter criteria and whilst indicating a greater level of certainty that the true value is below the target, it may mean that the true value has been below the target for some time.

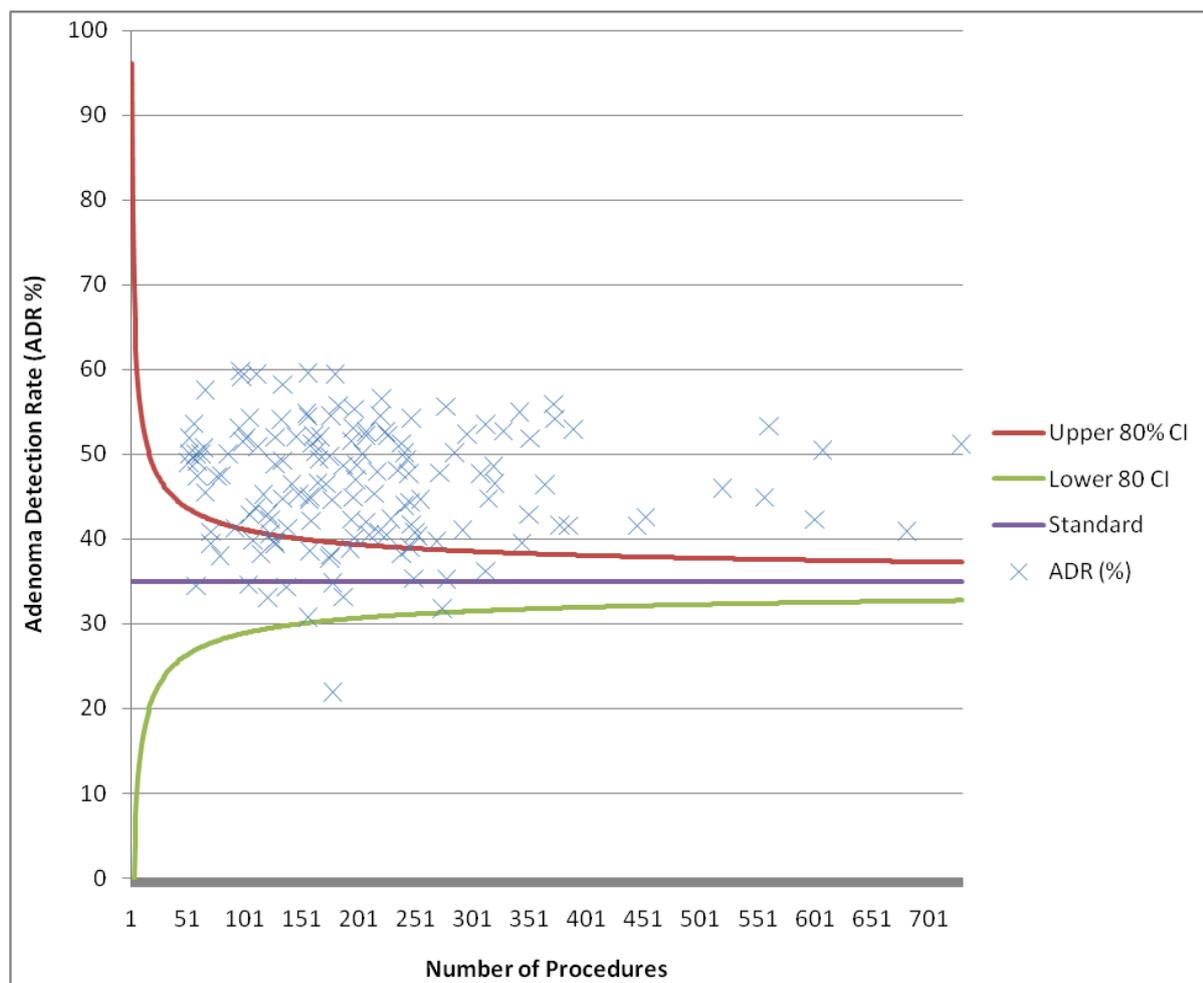


Figure 22- Funnel plot of ADR against number of procedures showing 80% confidence intervals around a minimum standard of 35%

Figure 22 shows an outlier with a low ADR. It was possible, using data generated for chapter 1, to be satisfied that this value was not an outlier due to missing data or age or gender variations in the colonoscoped population. Further action was taken by the BCSP through quality assurance channels to investigate and act upon this potential underperformance.

It became clear during the work for this thesis that whilst ADR was the most widely used and referenced performance indicator, quality assessment could not be confined to simply looking at adenoma detection. It is important to consider the safety of colonoscopy and the patient experience of colonoscopy at the same time as measuring technical aspects and lesion detection. One cannot be optimised at the expense of another. Figure 15 demonstrates a model of the components of assessing colonoscopy quality.

At present, colonoscopy quality assurance in the BCSP is largely focussed on lesion detection. Adverse event incidence is scrutinised at a local level, however, the minimum collected dataset for adverse events in the national database has limited analysis of trends in adverse events at a national level. Patient experience is poorly considered by the current quality assurance structure. This is mainly due to the lack of a validated, widely accepted measure of patient comfort during colonoscopy. Prospective validation of a Nurse Assessed Colonoscopy Comfort Score (NAPComs) has been undertaken at two centres in the North-east of England and a collaborating centre in Canada (Ross et al 2011) and results are awaited. Incorporation of this into quality assurance mechanisms of the BCSP may allow closer scrutiny of the patient experience. It should be considered that the patient experience of colonoscopy is not confined to comfort during the procedure itself.

In economics, Goodhart's Law states that "once a social or economic indicator or other surrogate measure is made a target for the purpose of conducting social or economic policy, then it will lose the information content that would qualify it to play such a role" (Goodhart 1975). This can be applied to colonoscopy performance indicators. For example, the data produced for chapter 1 contributed towards the BCSP Quality Assurance for Colonoscopy Guidelines (Chilton and Rutter 2011) defining the target for mean colonoscopy withdrawal time to be 10 minutes. This target will now affect the behaviour of colonoscopists and limit the use of withdrawal time to differentiate technical performance.

5.8.0- Specific recommendations to the Bowel Cancer Screening Programme

The following is a list of specific recommendations to the Screening Programme which have arisen from the work included in this thesis. A number of the recommendations have been acknowledged by the programme and incorporated into guidelines or routine practice:

1. Data quality measures:
 - a. Flags incorporated into BCSS software to alert users that an unexpected value has been entered.
 - b. Colonoscopists are given unique identifier codes
 - c. Entonox use should be recorded as a yes/no option rather than requiring a dose.
 - d. Standardisation of method for recording timing of colonoscopy
 - e. The definitions for colonoscopy quality indicators described in Appendix A should be utilized for routine reporting of colonoscopic performance in the BCSP.
2. Recording of adverse events- a standard classification system (Cotton 2010) should be employed.
3. There is no need to adjust for age, gender or screening round when routinely reporting measures of adenoma detection
4. Measures of total adenoma detection (MAP and MAP+) should be routinely reported in addition to ADR.
5. The proportion of procedures in which rectal retroversion is performed should not be used as a quality indicator of screening colonoscopy.
6. The optimal mean nc-CWT per colonoscopist for screening colonoscopy is around 10 minutes, this is now a quality target for colonoscopy in the BCSP.
7. Outlying performance by individual colonoscopists, as identified by measures of colonoscopic technical performance identified in this study, was investigated by the BCSP Quality Assurance group and local leads.
8. The following outcome measures should be audited for management of large sessile colonic polyps (LSCP):
 - a. The presence of malignancy in the endoscopic or surgical resection specimen
 - b. Incidence of complications (endoscopic or surgical)

- c. In the endoscopically managed group, the following outcomes were also analysed:
 - i. Need for surgery
 - 1. Due to detection of malignancy in the endoscopic resection specimen
 - 2. Because the lesion was no longer amenable to endoscopic management
 - ii. Presence of residual or recurrent polyp (RRP) at 12 months
- 9. Following endoscopic resection of LSCP in the BCSP, surveillance of the polypectomy site is conducted both at 3 months and at 12 months in keeping with existing guidelines and that the polypectomy site is routinely photographed (or videoed) and biopsied.
- 10. Consideration should be given to the creation of a network of expert colonoscopists to optimise clinical outcomes in difficult cases.

5.9.0- Reflections

I have discussed the strengths and weaknesses of this thesis in the discussion at the end of each chapter or subchapter. In this section I will reflect on a number of the general strengths and weaknesses of the thesis as a whole.

5.98.1- Data Quality

The Bowel Cancer Screening Programme commenced in 2006. Centralised data collection on all individuals passing through the programme was incorporated into the structure of the programme from the outset. The datasets were based on experience from the pilot studies and were not specifically designed to allow calculation of colonoscopy quality indicators. The user interface of the data collection system enforced very few mandatory fields and did not have any warning system if erroneous or unlikely values were entered.

Data entry was the responsibility of the Screening Practitioners who also had responsibility for counselling patients prior to colonoscopy and being present at colonoscopy. For many screening practitioners, uploading data was not a priority. As a result, there were concerns about the quality of the data and how it could be used to generate colonoscopy quality indicators.

My work with the national database to produce the data for chapter 1 of this thesis was the first time the national database had been used for researching colonoscopy quality. This was both positive and negative. The disadvantages were that the database was untried and untested. There were no processes for retrieving and processing the data. The quality of the data (in terms of completeness and accuracy) was not known. The quality indicators themselves (such as ADR and withdrawal time) had to be defined and the methods for converting raw data into meaningful figures or graphics which could be used both for research and as part of the quality assurance process needed describing. These problems were also advantages as working with the database for the first time allows a degree of freedom to tailor the definitions for the colonoscopy quality indicators and interpret the data in such a way that you know to be reliable and sound, as opposed to receiving data that has already been processed.

The data quality issue was addressed with a number of local audits comparing data from the national database with data held locally at a Screening Centre. These small audits showed satisfactory completeness and accuracy of the data. This perhaps, is a weakness of my work. The data verification and quality audits could have been larger and more rigorous and the findings were certainly limited by being confined to one screening centre. However, it was reassuring that the datafields necessary for calculating the key colonoscopy quality indicators were clearly well populated. The problems in the national database seemed to be with datafields where there was a degree of subjectivity (such as morphological shape of the lesion or therapeutic modality), or where there was a gap (either temporal or geographic) between the patient being screened and the relevant data being available for entry onto the database. An example of this is the cancer staging dataset, the use of which has been limited by poor data completeness.

I was also reassured that the data coming out the national database were reliable and reflected 'real-life' for four other reasons. Firstly, the initial work on the national database for Chapter 2.1, looking at outcomes at 12 month surveillance colonoscopy very closely mirrored findings from a pilot study I had performed at a regional level in the North East of England. Secondly, when I started to produce colonoscopy quality indicators from the national database, the results were similar to (but different on the grounds of variations in definition) figures that were already being produced around the country using locally held data. Thirdly, it became apparent very quickly when there was problem with the database. For instance, when a particular screening centre was shown to have a very low mean adenoma detection rate, further investigation of the database revealed missing information for three colonoscopists, reflecting poor data entry at the screening centre. Finally, the positive response I got from the screening community about the quality indicators that were being produced reassured me that there were not any major gaps in the data or major methodological flaws.

5.9.2- Data Collection

Whilst the data collection for chapter 1 was relatively straight forward, gathering data on the management of large sessile colonic polyps (LSCP) for chapter 2.2 was a more protracted affair. Because the detailed data on management was not available from the central database, it was necessary to obtain data from local screening centres. This required staff at the

screening centres to manually trawl the patients records for the necessary data. As the study was approved by the Evaluation Group of the BCSP, the screening centres were mandated to partake in the study, however, some centres with large numbers of polyps to return data on struggled to do so in within the planned time period. This was not helped by limited resources at some screening centres exacerbated by the increased workload generated by the age extension to 74 occurring around the same time. Despite this, thanks to the efforts of many screening practitioners, data were received for 93% of polyps. With hindsight, reducing the amount and simplifying the format of the data requested from each centre may have improved compliance and timeliness. In an ideal world, I would have collected the data from each centre personally. This however, would have been costly and time consuming and introduced the logistical difficulties of accessing data in different Trusts. If a similar exercise were performed in the future, it would be important to keep the requested dataset to a minimum and ensure the questions asked were objective and unambiguous. Ideally, the need to perform such a retrospective data collection could be avoided by prospectively gathering a minimum dataset on particular events, such as LSCP or adverse events.

5.9.3- Outcome Measures

In Chapter 1, adenoma detection rate is correlated with other measures of colonoscopy performance to justify its use as a marker of colonoscopic quality. These however, are indirect markers of colonoscopic quality. A direct association between ADR and interval cancer rate or adverse event incidence would be harder evidence to support the use of ADR as a marker of colonoscopic quality. Kaminski (2010) has demonstrated an association between ADR and interval cancer rates in the setting of the Polish screening programme. Measuring interval cancer rate is complicated by the difficulties in tracking patients who may be diagnosed with cancer outside the screening programme. The use of cancer registry data can facilitate this. Research is planned to produce interval cancer rates in the BCSP and thence to examine the relationship with baseline colonoscopy quality indicators at a colonoscopist level.

It was a planned component of this thesis to examine the relationship between ADR and adverse event incidence. I was unable to perform this analysis for two reasons. Firstly, adverse events are fortunately infrequent events. Most colonoscopists will have no or few adverse events attributed to them which limits statistical analysis with adverse events as the

dependent variable. Secondly, I was unable to produce adverse event data attributable to individual colonoscopists in the timeframe of this thesis. Whilst collecting data regarding the severity and circumstances of each adverse event was straight forward, it was not possible to identify the colonoscopist who performed the procedure at which the adverse event occurred, partly because the adverse event data was collected without a unique patient identifier in many cases and partly because screening centres were reluctant to provide an identifier of the colonoscopist. Further retrospective work to identify the colonoscopist associated with each adverse event would allow any association between ADR per colonoscopist and adverse event incidence to be examined. Alternatively, an identifier for the colonoscopist should be included in the minimum dataset collected for each adverse event.

5.9.4- Retrospective design

The type of analysis used in this thesis is retrospective and observational in nature. Such analysis is inherently at risk of bias due to residual confounding by imperfect measurement of confounders or by additional confounders not included in the analysis. To minimise the risk of bias, the work uses data prospectively collected for quality assurance purposes, which is generally of good quality, and most of the known or suspected confounding variables are adjusted for in the analyses. The gold-standard methodology for testing an hypothesis such as ‘colonoscopy withdrawal time is not associated with adenoma detection rate,’ would be a prospective randomised controlled trial (RCT). Blinding in endoscopy trials is difficult for obvious reasons. Such trials would need to be large and expensive and would be difficult to justify ethically when the positive benefits of longer withdrawal is apparent for observational data.

RCTs are designed to test the effect of a difference between two populations whilst prospectively adjusting for known confounding factors. Retrospective studies do not allow this luxury and therefore have a tendency to raise as many questions as they answer.

An example of the difficulty of proving the benefit of endoscopic technique in terms of increased adenoma detection is demonstrated by a planned prospective randomised controlled trial of Buscopan use with normal saline in the placebo arm. A prospective study was estimated to cost a minimum of £250,000 to run. It is therefore much easier to perform a retrospective study, as we have done in chapter 1, to answer the question.

5.9.5- Non-technical endoscopy skills

A confounding variable that I have been unable to account for when examining colonoscopic performance may be the non-technical skills of the colonoscopist. Currently, colonoscopy performance indicators reflect easily measurable, objective aspects of colonoscopic technique such as colonoscopy withdrawal time. Non technical skills of endoscopy have been recently described by Haycock (2010) and others and reflect the subjective aspects of colonoscopic performance. The skills fall into 5 main categories: Communication and teamwork, situation awareness, leadership, judgment and decision making. These factors are difficult to measure but may contribute to performance measures such adenoma detection. Other factors such as fatigue (Harewood 2008), concentration, visual recognition patterns and attitudinal beliefs may also contribute. Looking to the future, the ability to measure non-technical skills may allow their contribution to adenoma detection to be examined.

5.9.6- External validity

A major limitation of the work in this thesis is that the findings are strictly only relevant to the population in which the measurements were made, that is FOBt positive English adults aged 60 or over. The main reasons the external validity of these findings may be limited are firstly, that the population undergoing colonoscopy have a very high neoplastic burden. The adenoma detection rates observed in Chapter 1 of this thesis are amongst the highest rates reported in the international literature. Some of the conclusions of the thesis, such as recommending a mean withdrawal time of around 10 minutes or using measures of total adenoma detection, have limited relevance to colonoscopy in an average risk population or a symptomatic population such as in day to day practice in the NHS. Colonoscopy in symptomatic or average risk populations is associated with much lower adenoma detection rates. This limitation has proved an issue with trying to get the findings of the thesis published in US Journals. On two occasions the reviewers have noted that findings in an FOBt positive population may be of limited relevance to primary screening colonoscopy in the USA.

5.9.7- Future research

The following studies would contribute to answering questions raised by the work in this thesis:

1. Correlation of colonoscopy performance indicators with interval cancer rates in the NHS Bowel Cancer Screening Programme.
2. Correlation of measures of adenoma detection (MAP and MAP+) with existing measures of colonoscopic performance (CIR, CWT, PRR).
3. Does ADR improve if CWT increases- an observational study of BCSP colonoscopists?
4. Is there a learning curve in BCSP colonoscopy?
5. Randomised control trial of buscopan vs. placebo, outcome measures-ADR and MAP
6. Randomised trial of endoscopic vs. surgical management of large sessile colonic polyps.
7. A systematic review and metaanalysis of the effect of time of day on adenoma detection at colonoscopy.

General Summary

1. The NHS Bowel Screening Programme National Database contains quality data which can be used to calculate colonoscopy performance indicators.
2. Adenoma detection rate per colonoscopist correlates positively with other measures of colonoscopy performance such as colonoscopy withdrawal time and caecal intubation rate.
3. These measures of performance can also be used as quality indicators. The NHS Bowel Cancer Screening Programme offers high quality colonoscopy.
4. Measures of total adenoma detection such as MAP (mean number of adenomas per procedure) and MAP+ (mean number of adenomas per positive procedure) can enhance quality assurance of colonoscopy in the BCSP.
5. The optimum mean withdrawal time per colonoscopist is around 10 minutes.
6. Patient age, gender, smoking status, alcohol use, socioeconomic status and geographical location are associated with the risk of adenoma, right sided adenoma and advanced adenoma detection in multivariable analysis.
7. In the same analysis, colonoscopy factors including withdrawal time, caecal intubation, bowel preparation quality, antispasmodic use, colonoscopist experience and time of day are associated with adenoma, right sided adenoma and advanced adenoma detection.
8. Prolonging withdrawal time, using antispasmodics and optimising bowel preparation quality are easily modified factors that may improve adenoma detection rate but this would need prospective studies to prove.
9. 12 month surveillance of patients with 'high risk' adenomas at baseline screening is associated with a yield of advanced adenomas or cancers that justify this surveillance interval.
10. The presence of right sided or villous adenomas at baseline screening is associated with increased risk of advanced neoplasia at 12 month surveillance. Analyses of these factors in larger datasets and those undergoing 3 year surveillance may allow surveillance criteria to be refined.

11. Larger and right-sided large sessile or flat colonic polyps (LSCP) are more likely to be managed surgically in the first instance. Increasing size of the LSCP is associated with failure of endoscopic therapy, subsequent need for surgery and presence of cancer in the resection specimen.

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Appendix A- Definitions of Colonoscopy Quality Indicators

The following variables are commonly used indicators of colonoscopic quality. They were assessed (where appropriate) at the following levels:

- Screening centre
- Endoscopy Unit
- Individual colonoscopist.

Data were predominately gathered by analysing the BCSS database. Further details of this are provided in the Methodology section. Specific definitions of the variables and consideration of the raw data held in the database are given below.

A.1- Adenoma detection rate

Adenoma detection rate (ADR) was defined as:

- Numerator : The number of colonoscopies at which one or more histologically confirmed adenomas were found (in a given time period).
- Denominator: Total number of colonoscopies performed (in the same time period).

Within the context of the BCSP the following rules will apply:

- Only histologically proven adenomas, the details of which have been uploaded onto the BCSP database will be counted.
- Only first screening colonoscopies will be counted. Surveillance and therapeutic procedures will not be included in the analysis.
- Incomplete (not reached caecum) colonoscopies will be included in the analysis.
- All colonoscopies fitting the 2 criteria above, regardless of outcome, will be included in the denominator count.

ADR was calculated (for a predefined time period and colonoscopist or location) using the following data fields from the BCSS database: (text in square brackets refers to specific data fields in the database).

- Numerator: Count of colonoscopies where [Count of Adenomas] \geq 1
- Denominator: Count of colonoscopies performed.
- Only adenomas were counted- [Count of Adenomas] = Number of polyps with [Polyp_Type] = adenoma.
- Only screening colonoscopies were counted- [Investigation.Confirmed_Type_of_Test] = Colonoscopy AND [Investigation.Episode_Type] = Screening

The following fields were used to define the timeframe, location or colonoscopist.

- Date of procedure - [Investigation.Confirmed_Date_of_Test]
- Site of procedure - [Investigation.External_Test_Site_ID]
- Colonoscopist - [Investigation.External_Test_Consultant_ID]

A.2- Colonoscopy withdrawal time

Colonoscopy withdrawal time (CWT) is defined as the average time taken by a particular endoscopist withdrawing the colonoscope from the caecum to extubation from the anus. Only procedures which were 'normal' (i.e. no therapeutic procedures were undertaken) and at which the caecum was reached were be counted in the analysis. Screening or surveillance procedures (but not therapeutic procedures) were included.

The following data fields are routinely recorded by the Screening Practitioner during the procedure and uploaded onto the BCSS database:

- [Investigation_Colonoscopy.QA_Start_Time]
- [Investigation_Colonoscopy.QA_Finish_Time]
- [Investigation_Colonoscopy.QA_Withdrawal_Time]- This field will be used to calculate the mean CWT.

The following rules will apply to which colonoscopies are included:

Screening or Surveillance subject episodes only – [Investigation.Episode_Type] = Screening or Surveillance.

- Subjects who had a colonoscopy - [Investigation.Confirmed_Type_Of_Test] = Colonoscopy.
- Where the colonoscopy was complete - [Investigation_colonoscopy.QA_Extent] = Caecum, Ileum or Appendix.
- Where the result of the colonoscopy was normal – [Investigation.Diagnostic_test_result] = Normal
- Confirm that the result of the colonoscopy was normal – [Investigation_colonoscopy.Number_Polyps_Resected] = 0 or blank

The following fields were used to define the timeframe, location or colonoscopist.

- Date of procedure - [Investigation.Confirmed_Date_of_Test]
- Site of procedure - [Investigation.External_Test_Site_ID]
- Colonoscopist - [Investigation.External_Test_Consultant_ID]

A.3- Caecal intubation rate

Caecal intubation rate (CIR) was defined as:

- Numerator – Number of colonoscopies at which the caecum or terminal ileum was reached in a stated period.
- Denominator – Total number of colonoscopies performed in the same period.

Screening practitioners record the completeness of the colonoscopy during the procedure and upload this onto the Database. An ‘intention to reach caecum’ approach was used. All failures were counted regardless of the reason.

Both screening and surveillance colonoscopies were included. Only subjects who had one test in each screening round were included (to avoid counting repeat procedures).

The following fields on the BCSS database were used:

Extent of procedure – [Investigation_Colonoscopy.QA_Extent] = caecum, appendix or ileum.

The following rules will apply to which colonoscopies are included in the analysis:

- Screening and surveillance subject episodes – [Investigation.Episode_Type] = Screening or Surveillance.
- Subjects who had a colonoscopy- [Investigation.Confirmed_Type_Of_Test] = Colonoscopy
- Where the subject only had 1 procedure in the episode - Where count of [Confirmed_Type_Of_Test] = 1 per [Episode_ID]

The following fields will be used to define the timeframe, location or colonoscopist.

- Date of procedure - [Investigation.Confirmed_Date_of_Test]
- Site of procedure - [Investigation.External_Test_Site_ID]
- Colonoscopist - [Investigation.External_Test_Consultant_ID]

A.4- Rectal retroversion

Rectal retroversion is a recommended procedure to ensure lesions at the anorectal junction are not missed. It is a marker of completeness of the colonoscopic examination.

All screening and surveillance colonoscopies were included in this analysis. Only subjects undergoing one colonoscopy in each round were included to avoid double counting repeat procedures.

Rectal retroversion rate was defined as:

- Numerator – Number of colonoscopies during which rectal retroversion is performed
- Denominator – Total number of colonoscopies performed.

The following database field was used for the numerator;

- Was retroversion performed? - [QA_Retro] = Yes

The following rules will apply to which colonoscopies are included in the analysis:

- Screening and surveillance subject episodes – [Investigation.Episode_Type] = Screening or Surveillance.
- Subjects who had a colonoscopy- [Investigation.Confirmed_Type_Of_Test] = Colonoscopy
- Where the subject only had 1 procedure in the episode - Where count of [Confirmed_Type_Of_Test] = 1 per [Episode_ID]

The following fields were used to define the timeframe, location or colonoscopist.

- Date of procedure - [Investigation.Confirmed_Date_of_Test]
- Site of procedure - [Investigation.External_Test_Site_ID]
- Colonoscopist - [Investigation.External_Test_Consultant_ID]

A.5- Sedation practices

Sedation doses used and patient comfort during each colonoscopy are recorded by the Screening Practitioner and uploaded on the database.

All colonoscopies will be included in the analysis in the section.

The following database fields will be used: (text in square brackets refers to specific data fields in the database, text in curly brackets –{ }, refers to the variables):

- Nurse assessment of patient comfort during procedure – [QA_Comfort_Exam] = { No or minimal discomfort, Mild discomfort, Moderate discomfort, Severe discomfort }
- Mean doses of the following drugs used by each colonoscopist
 - Midazolam
 - Fentanyl
- Number (and proportion) of procedures in which no sedation was used (ie no benzodiazepines or opiates were recorded as having been used).

A.6- Patient Comfort

Nurse reported patient comfort score is recorded contemporaneously by the screening practitioner at two points during the patient's journey through colonoscopy. Firstly 'during the examination' and secondly, 'in recovery'.

Patient comfort (or discomfort) is scored on a modified Likert scale as one of 4 options {none or minimal discomfort, mild discomfort, moderate discomfort, severe discomfort}.

Although this is not a validated method of recording patient comfort and the data is limited by being nurse- (rather than patient-) reported, the proportion of patients in each category will indicate comfort levels in each colonoscopist's cohort of patients.

All procedures will be included in the analysis for this quality indicator.

The following fields will be used:

- [QA_Comfort_Exam]
- [QA_Comfort_Recovery]

Patient comfort is graded on the following scale at each time point:

- {No or minimal discomfort}
- {Mild discomfort}
- {Moderate discomfort}
- {Severe discomfort}

Data will be presented as the percentage of patients in each category per colonoscopist.

A.7- Bowel preparation quality

Adequate bowel preparation is a prerequisite for a high quality colonoscopy. Quality of bowel preparation is recorded at the time of colonoscopy and uploaded onto the BCSP database.

The following data field and variables are used:

- [QA_Bowel_Prep]
 - {Excellent}
 - {Adequate}
 - {Complete examination despite inadequate preparation}
 - {Incomplete examination due to inadequate preparation}

All colonoscopies including screening, surveillance and therapeutic procedures will be included.

Data will be analysed at the following levels:

- Site of procedure - [Investigation.External_Test_Site_ID]

A.8- Adverse events

Complications are recorded on the BCSP database and classified as either being early or late. The following complications are recorded:

Early Complications	Late Complications
Pain	Pain
Hypoxia	Haemorrhage
Bradycardia	Perforation of colon
Iatrogenic hypotension	Aspiration pneumonia
Cardiac arrhythmia	Death
Cardiac arrest	Fever and sweats
Respiratory arrest	Bleeding
Haemorrhage	Bleeding requiring transfusion
Perforation of colon	Anaphylactic reaction
Consent refused	
Aspiration pneumonia	
Death	
Withdrawal of consent	
Bleeding	
Bleeding requiring transfusion	
Anaphylactic reaction	
Use of reversal agent	

Table 43- Classification of colonoscopy adverse events in the BCSP

The following data fields will be used:

- [Complication_early]
- [Complication_late]
- Was the patient discharged home after the procedure or kept in hospital? - [QA_Outcome] – {Discharge Home} or {Unscheduled emergency hospital admission}.

Data will be presented as follows:

- Number of Early complications
- Number of Late complications
- Number of times reversal agents (flumazenil or naloxone) were used
- Number of colonic perforations
- Number of bleeding episodes (Number requiring transfusion)
- 30 day mortality.

The classification of adverse events described above has largely been superseded by the stratification according to severity described in figure 10.

A.9- Polyp Retrieval Rate

As many polyps as possible should be retrieved once they have been removed to allow histological examination to establish the nature of the polyp as this will impact on subsequent management. Polyp retrieval relies on adequate technical skills of the colonoscopist and thus is a marker of the technical quality of the colonoscopy.

Polyps which are not retrieved are recorded on the screening database as such.

Polyps retrieval rate is calculated as follows:

Numerator: Number of polyps retrieved

Denominator: Total number of polyps removed

The following fields are used:

- Was the polyp retrieved? [Polyp_Therapy_Success]
 - {Biopsy specimen not retrieved}
 - The number of polyps retrieved (ie the numerator) will be calculated by subtracting the number of polyps not retrieved from the total number of polyps discovered.

The following rules will apply to which colonoscopies are included in the analysis:

- Screening and surveillance subject episodes – [Investigation.Episode_Type] = Screening or Surveillance.

Appendix B- Ethical approval



National Research Ethics Service

County Durham & Tees Valley 2 Research Ethics Committee

The Tatchell Centre
University Hospital of North Tees
Piperknowle Road
Stockton-on-Tees
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17 September 2009

Dr T Lee
Endoscopy Research Fellow
University Hospital of North Tees
Piperknowle Road
Stockton-on-Tees TS19 8PE

Dear Dr Lee

Full title of project: Detection and management of colorectal neoplasia in the NHS Bowel Cancer Screening Programme

Thank you for seeking the Committee's advice about the above project.

You provided the following documents for consideration:

Covering letter dated 15 September 2009

Project Plan dated September 2009

This document has been considered by the Chair, who has advised that the project does not require ethical review by a NHS Research Ethics Committee.

This letter should not be interpreted as giving a form of ethical approval to the project or any endorsement of the project, but it may be provided to a journal or other body as evidence that ethical approval is not required under NHS research governance arrangements.

However, if you, your sponsor/funder or any NHS organisation feels that the project should be managed as research and/or that ethical review by a NHS REC is essential, please write setting out your reasons and we will be pleased to consider further.

Yours sincerely

Leigh Pollard

Committee Co-ordinator

Appendix C- Dissemination

Efficacy and safety of colonoscopy in the UK NHS Bowel Cancer Screening Programme

Published by GUT, 2011 [Epub ahead of print]

Plenary oral presentation – BSG March 2011

Poster – DDW May 2011

Oral Presentation – International Coloproctology Forum, Verbier, January 2011

Colonoscopy withdrawal time and adenoma detection rate in screening colonoscopy:

The optimum average withdrawal time is 10 minutes

Pending revisions for Endoscopy February 2012

Rejected after review by NEJM on January 2011 and Gastrointestinal Endoscopy August 2011

Oral presentation - BSG March 2011

Oral presentation - DDW May 2011

Patient and colonoscopy factors influencing adenoma detection in patients undergoing colonoscopy in the NHS Bowel Cancer Screening programme

Poster – BSG March 2011

Awarded Best paper presented by a trainee in the surgical section at the BSG

Oral presentation - DDW May 2011

12 month surveillance colonoscopy for high risk adenomas in the NHS Bowel Cancer Screening Programme

Oral presentation - Institute of Health and Society Research Day July 2010

Oral presentation - Royal Society of Medicine (Coloproctology Section) Overseas Meeting, Krakow, Poland, June 2010

Poster – BSG March 2010

Management of large colonic polyps in the NHS Bowel Cancer Screening Programme

Under review, Endoscopy, February 2012

Oral presentation - BSG March 2011

Can we improve on ADR as a measure of colonoscopic quality- MAP and MAP+?

Oral presentation - BSG March 2011

Poster – DDW May 2011

Colorectal Polyp Cancers in the NHS Bowel Cancer Screening Programme.

Poster - NCRI November 2010

Shortlisted for the British Oncology Association Young Investigator award.

Appendix D- Abbreviations

ACN	Advanced colonic neoplasia
ADR	Adenoma detection rate
AE	Adverse events
APC	Adenomatous polyposis coli
AS-ADR	Age standardised adenoma detection rate
BCSP	Bowel Cancer Screening Programme
BCSS	Bowel Cancer Screening System
BMI	Body mass index
CI	Confidence intervals
CIR	Caecal intubation rate
COX 2	Cyclo-oxegenase 2
CRC	Colorectal cancer
CWT	Colonoscopy withdrawal time
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
EUS	Endoscopic ultrasound
FAP	Familial adenomatous polyposis
FOBt	Faecal occult blood testing
GS-ADR	Gender standardised adenoma detection rate
HD	High definition
HGD	High Grade dysplasia
HNPCC	Hereditary non polyposis colorectal cancer
I1-ADR	First incident round ADR
I2 ADR	Second incident round ADR
IBD	Inflammatory Bowel Disease
ICC	Intra class correlation coefficient
IMD	Indicies of multiple deprivation
JAG	Join advisory group on endoscopy
kg	kilogram
LGD	Low grade dysplasia
LSCP	Large sessile or flat colonic polyps

LSoA	Lower Super output Area
MAP	Mean number of adenomas per patient
MAP+	Mean number of adenomas per positive procedure
NapComs	Nurse assessed patient comfort score
NBI	Narrow band imaging
NC-CWT	Negative complete colonoscopy withdrawal time
NHS	National Health Service
N/R	Nor recorded
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
P-ADR	Prevalent round ADR
PDR	polyp detection rate (PDR)
PIAG	Patient Information Advisory group
PJS	Peutz-Jeghers Syndrome
PRR	Polyp retrieval rate
PYO	Person years of observation
RCT	Randomised control trial
RR	Relative risk
RRP	Residual or recurrent polyp
RRR	Rectal retroversion Rate
sd	Standard deviation
TEMS	Trans-anal Endoscopic Micro-Surgery
TNM	Tumour, Node, Metastases
uCIR	unadjusted Caecal intubation rate
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation