

**Genetic, clinical and pathological factors in
management and surveillance of patients with
colorectal tumours**

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Summary

Numerous factors influence an individual's risk of colorectal cancer, including pathological features such as polyp size and multiplicity, and family history of colorectal malignancy. In clinical practice polyp size can be measured at different time points, however adenoma surveillance guidelines do not define which measurement to utilise, due to variance in data source. The initial study compared the measurements of 107 polyps. Variation in surveillance intervals occurred less frequently with post-fixation than in situ measurements (5.6 versus 9.5%), supporting the use of post-fixation polyp size. A further study considered the level of agreement amongst histopathologists in Wales in the reporting of colorectal polyps. Only fair agreement ($k = 0.24$) was observed in the reporting of the completeness of excision. A lesion with epithelial misplacement and high grade dysplasia was misclassified as adenocarcinoma by five pathologists, indicating the need for further training and potential introduction of a formal accreditation process.

Individuals with a moderate family history risk of colorectal cancer are at increased risk of colorectal lesions. Pathways through the Welsh genetics service were studied. 63.4% referrals were received from primary care. The majority of patient's were female (70.8%). 93.8% patients were advised to undergo 5-yearly surveillance. Existing referral pathways were found to be complex increasing the risk of over/under surveillance. Little is known about colonoscopic surveillance outcomes following genetic assessment. A study of 172 patients revealed an adenoma detection rate (ADR) of 11.1% and advanced ADR of 4.1% at the index procedure. Cancer was diagnosed in 0.6% cases. The majority of lesions identified were diminutive low grade adenomas. Several endoscopic modalities have been utilised to enhance polyp detection in patients with a propensity to colonic polyps. Narrow band imaging was studied in 37 high-moderate risk patients, but did not significantly increase polyp yield above high definition white light colonoscopy.

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List of abbreviations

AFAP	Attenuated Familial Adenomatous Polyposis
AFI	Autofluorescence Imaging
ADR	Adenoma Detection Rate
APC	Adenomatous Polyposis Coli
BCSP	Bowel Cancer Screening Programme
BRAF	Serine/threonine-protein kinase B-Raf
CCD	Charged Couple Device
CHIRP	Cancer Histopathology Reporting Project
CI	Confidence Interval
CIN	Chromosomal Instability
CIMP	CpG Island Methylation Phenotype
CIMP-H	CpG Island Methylation High Phenotype
CIMP-L	CpG Island Methylation Low Phenotype
CP	Capillary Pattern
CVC	Computed Virtual Chromoendoscopy
DCC	Deleted in Colorectal Carcinoma
DNA	Deoxyribonucleic Acid
EMR	Endoscopic Mucosal Resection
ESD	Endoscopic Submucosal Dissection
FAP	Familial Adenomatous Polyposis
FDR	First Degree Relative
FICE	Fujinon Intelligent Chromoendoscopy
FOB	Faecal Occult Blood
GCSP	Goblet Cell Serrated Polyp

GDP	Guanosine-5'-Diphosphate
GP	General Practitioner
GTP	Guanosine Triphosphate
HD	High Definition
HNPCC	Hereditary Non – polyposis Colorectal Cancer
HPS	Hyperplastic Polyposis Syndrome
IC	Indigo carmine
IHC	Immunohistochemistry
K – ras	Kirston Rat Sarcoma viral oncogene homolog
Mag	Magnification endoscopy
MAP	MutYH – Associated Polyposis
MMR	Mismatch Repair
MSI	Microsatellite Instability
MSI - H	Microsatellite Instability - High
MSI - L	Microsatellite Instability - Low
MSS	Microsatellite Stable
MVSP	Microvesicular Serrated Polyp
NBI	Narrow Band Imaging
NHS	National Health Service
NPS	National Polyp Study
OR	Odds Ratio
PEG	Polyethylene Glycol
RGB	Red, Green, Blue
RR	Relative Risk
SDR	Second Degree Relative
SE	Surface Enhancement

SEER	Surveillance, Epidemiology and End Result
SIR	Standardised Incidence Ratio
SPS	Serrated Polyposis Syndrome
SSA	Sessile Serrated Adenoma
TP	Tumour Protein
TSA	Traditional Serrated Adenoma
WCISU	Welsh Cancer Intelligence and Surveillance Unit
WHO	World Health Organisation

Table of Contents

Declaration	II
Summary	III
Acknowledgements	IV
List of Abbreviations	V
Table of Contents	VIII
<u>Chapter 1: Introduction and background</u>	1
1.1 Colorectal Cancer Epidemiology	1
1.2 Pathways to Colorectal Cancer	2
1.2.1 Molecular Genetic Pathways to Colorectal Carcinogenesis	3
1.2.2 Histopathological Evidence for Colorectal Carcinogenesis	7
<i>1.2.2.1 Polyp Type and Grade of Dysplasia</i>	8
<i>1.2.2.2 Polyp Size</i>	9
<i>1.2.2.3 Polyp Multiplicity</i>	9
1.2.3 Serrated Pathway	10
1.2.4 Polyp Morphology	12
<i>1.2.4.1 Flat Lesions</i>	14
1.3 Rationale for Colonoscopic Screening and Surveillance	15
1.3.1 Evidence for Polyp Progression and Regression	15
1.3.2 Effect of Polypectomy on Colorectal Cancer Risk	16
1.3.3 Rationale for Post Polypectomy Surveillance	17
1.3.4 Polyp Miss Rates	18
1.3.5 Adenoma Detection Rates (ADRs)	19
1.3.6 Adenoma Prevalence Rates	20

1.4	Colorectal Cancer Risk Groups	20
1.4.1	Average Risk Group	21
1.4.2	High Risk Groups	21
	<i>1.4.2.1 Familial Adenomatous Polyposis (FAP)</i>	21
	<i>1.4.2.2 Hereditary Non-Polyposis Colorectal Cancer (HNPCC)</i>	22
	<i>1.4.2.3 Human MutY homologue (MUTYH) Associated Polyposis (MAP)</i>	23
	<i>1.4.2.4 Serrated Polyposis Syndrome</i>	24
1.4.3	Moderate Risk Group	25
1.5	Medical and molecular genetics in the management of moderate risk groups	28
1.5.1	Accuracy of Data Collection	28
1.5.2	Surveillance Compliance	29
1.6	Endoscopic Optimisation of Polyp Detection	29
1.6.1	Chromoendoscopy (Dye Spray)	30
1.6.2	Digital Chromoendoscopy	33
	<i>1.6.2.1 Narrow Band Imaging (NBI)</i>	34
	<i>1.6.2.2 Fujinon Intelligent ChromoEndoscopy (FICE)</i>	37
	<i>1.6.2.3 I-Scan</i>	38
	<i>1.6.2.4 Autofluorescence Imaging (AFI)</i>	38
1.6.3	High Definition Imaging	40
1.7	Factors Affecting the Quality and Yield of Colonoscopy	41
1.7.1	Bowel Cleansing	41
1.7.2	Antispasmodic Agents	42
1.7.3	Position Change and Luminal Distension	43
1.7.4	Withdrawal Technique and Rectal Retroflexion	44
1.7.5	Colonoscope Withdrawal Times	45

1.8	Risks of Colonoscopy	46
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Chapter 2: Accuracy and concordance between in situ and post-fixation measurements of colorectal polyp size and their potential impact upon surveillance intervals

2.1	Background	48
2.2	Study aims	49
2.3	Ascertainment of cases and methodology	49
2.3.1	Statistical analysis	51
2.4	Results	52
2.5	Discussion	59

Chapter 3: Interobserver agreement in the reporting of colorectal polyp pathology among histopathologists in Wales

3.1	Background	64
3.2	Study aims	65
3.3	Ascertainment of cases and methodology	65
3.3.1	Statistical analysis	68
3.4	Results	69
3.5	Discussion	74

<u>Chapter 4: Referral pathways through a regional medical genetics service</u>	
<u>in patients with a moderate family history risk of colorectal cancer</u>	82
4.1 Background	82
4.2 Study aims	84
4.3 Ascertainment of cases and methodology	84
4.4 Results	85
4.5 Discussion	89
<u>Chapter 5: Colonoscopic surveillance outcomes in patients with a</u>	
<u>moderate family history risk of colorectal cancer</u>	95
5.1 Background	95
5.2 Study aims	96
5.3 Ascertainment of cases and methodology	96
5.4 Results	97
5.5 Discussion	102
<u>Chapter 6: Narrow band imaging in the surveillance of patients</u>	
<u>with a moderate family history risk of colorectal cancer</u>	106
6.1 Background	106
6.2 Study aims	107
6.3 Methodology	108
6.3.1 Ascertainment of cases	108
6.3.2 Statistical analysis	110
6.3.3 Study approval	110
6.4 Results	111
6.5 Discussion	113

<u>Chapter 7: Concluding discussion and future prospects</u>	120
<u>References</u>	124
<u>Appendices</u>	145
Appendix 1	146
Appendix 2	147
Appendix 3	150
<u>Publications and presentations relating to this work</u>	153
Publications	153
Oral presentations	154
Poster presentations	155

1. Introduction and background

1.1 Colorectal Cancer Epidemiology

Colorectal cancer is the third most common cancer worldwide, with an estimated 1,235,108 new cases (10% of the total number of cancer diagnoses) in 2008 (Globocan 2008). Nearly two thirds (60%) of these were diagnosed in developed countries. Colorectal cancer is also estimated to account for 609,051 (8.1%) of all cancer deaths for the same time period. The incidence is higher in men than women (ratio 1.4:1.0), as is the age-standardised mortality ratio.

Throughout Europe, colorectal cancer forms between 13 - 14% of all cancer cases, with the second highest reported incidence and mortality rates (Ferlay et al. 2007; Globocan 2008) (Figure 1).

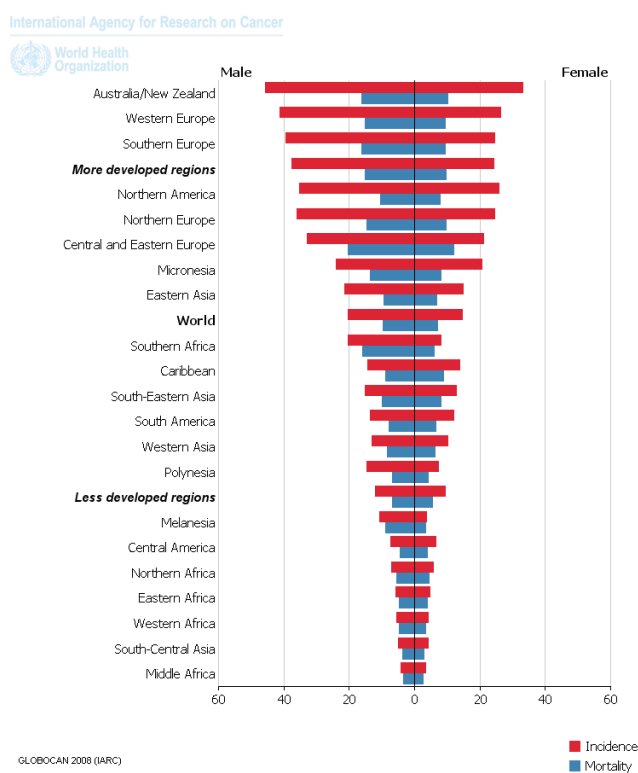


Figure 1 Estimated age-standardised rates (World) per 100,000 (Globocan 2008).

The lifetime risk of colorectal cancer within the UK is approximately 1 in 15 for men and 1 in 19 for women (Cancer Research UK 2012). 41,142 new cases of colorectal cancer were reported in 2009, which equates to an age standardised incidence rate of 47.7 per 100,000 population (Cancer Research UK 2012). This fell slightly to 46.6 per 100,000 population in 2010. There has been a steady fall in the age standardised mortality rate over the last twenty years, from 27.1 per 100,000 population in 1980 to 16.8 per 100,000 in 2010 (Cancer Research UK 2012).

A total of 11,281 cases of colorectal cancer were diagnosed in Wales between 2006 - 2010 (6578 cases between 2006 - 2008 and 6949 cases between 2008 - 2010) (Welsh Cancer Intelligence and Surveillance Unit (WCISU) 2012a). Incidence data using European age standardised rates per 100,000 population have shown a slight increase in cases from 62.0 in 2000 to 67.6 in 2010 for men, compared with 35.3 in 2000 to 35.8 in 2010 for women (WCISU 2012b).

The most recently published longer-term mortality data have shown a fall in the total number of deaths from colorectal cancer from 1032 in 1995 to 932 in 2004 (WCISU 2004). The WCISU have estimated the projected number of cases and deaths from colorectal cancer for 2014 – 2018, using statistical modelling (White et al. 2006). It is estimated that 2752 new cases of colorectal cancer will be diagnosed per year over this time interval. The number of deaths per year for colorectal cancer is estimated at 942.

1.2 Pathways to Colorectal Cancer

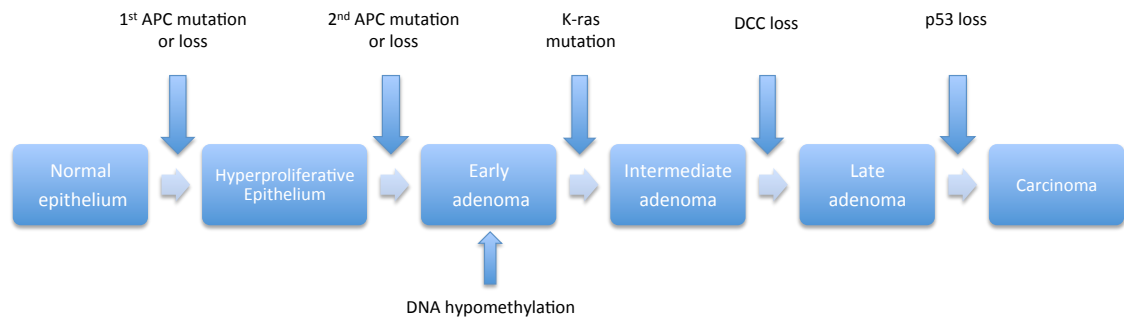
The suggestion that colorectal polyps may progress to cancer dates back to the 1950's. Jackman and Mayo (1951) proposed an 'adenoma-carcinoma' sequence based upon several observations: (i) untreated polyps demonstrated carcinoma on follow up

examinations, (ii) a high proportion of patients with ‘familial multiple polyposis’ died of cancer and (iii) the location and distribution of polyps within the colon was similar for carcinoma. However it was not until over 20 years later that histological and radiological studies were published to support such a pathway (Muto et al. 1975; Stryker et al. 1987). More recently, molecular genetic studies have provided evidence of progression of conventional and serrated adenomas to carcinoma.

1.2.1 Molecular Genetic Pathways to Colorectal Carcinogenesis

Until the 1980’s evidence for the adenoma-carcinoma sequence was largely based upon epidemiological data. Vogelstein et al. (1988) studied 172 colorectal specimens (80 adenomas and 92 carcinomas) for *ras*-gene mutations and evidence of deletions on chromosome 5q which contains the ‘Adenomatous Polyposis Coli’ (APC) tumour suppressor gene, chromosome 17p containing the p53 tumour suppressor gene and chromosome 18q containing the ‘Deleted in Colorectal Carcinoma’ (DCC) gene. The authors identified the majority (88%) of mutations detected in carcinomas to be of the K-ras gene. The percentage of *ras*-gene mutations increased with grade of dysplasia and size of the polyp. No gene deletions occurred on chromosome 5q in patients with FAP, but occurred in 29 – 36% of patients with non-FAP adenomas or carcinomas. Chromosome 18 deletions occurred most frequently in advanced adenomas (47%) and carcinomas (73%), compared with chromosome 17 where deletions tended to occur in carcinomas (75%). A series of genetic alterations of these oncogenes and tumour suppressor genes is thought to result in transformation of adenomas through to carcinoma. With data from this study, the authors proposed a multi – step genetic model several years later (Fearon and Vogelstein 1990) (Figure 2). The number of genetic alterations increases as lesions progress from adenomas, to adenomas with a focus of adenocarcinoma and eventually to carcinoma (Vogelstein et al. 1988). 7% of early

adenomas had ≥ 1 genetic alteration, compared with carcinomas where ≥ 2 alterations occurred in more than 90% of cases (Fearon and Vogelstein 1990).



(APC: Adenomatous polyposis Coli; DCC: Deleted in Colorectal Carcinoma gene; DNA, Deoxyribonucleic Acid)

Figure 2 Multi - step genetic model.

There are now thought to be at least three principal pathways to colorectal carcinogenesis, which have been defined since the multi-step genetic model was described (Fearon and Vogelstein 1990):

(1) Chromosomal Instability (CIN) pathway:

Chromosomal instability is estimated to occur in up to 85% of colorectal cancers (Grady 2004). This pathway consists of mutations of tumour suppressor genes (APC, p53, DCC) and oncogenes (K - ras). The protein produced by the tumour suppressor gene APC (adenomatous polyposis coli) suppresses the Wnt-signalling pathway, which is responsible for regulating cell growth and apoptosis (Cadigan and Liu 2006). p53 is a transcription factor encoded for by the TP53 (tumour protein) gene that can activate DNA repair proteins, hold the cell cycle allowing DNA repair and can initiate apoptosis where appropriate.

The K - ras proto-oncogene encodes the protein K - ras (Kirsten rat sarcoma viral oncogene homolog). This protein normally binds to Guanosine-5'-Triphosphate (GTP) converting it to Guanosine Diphosphate (GDP), forming an essential part of normal tissue signalling. Mutation of this gene causes persistence of the active GTP protein, resulting in continued cell division signalling.

(2) Microsatellite Instability (MSI) Pathway:

Microsatellites are sequences consisting of 1 – 5 base pairs, repeated throughout all deoxyribonucleic acid (DNA) (Wheeler et al. 2000). During DNA replication the microsatellites can mutate, requiring repair by mismatch repair (MMR) enzymes. Mutation of the genes responsible for the MMR enzymes results in accumulation of microsatellite mutations and microsatellite instability (MSI).

The term MSI was coined following several independently published articles in 1993 (Aaltonen et al. 1993; Ionov et al. 1993; Thibodeau et al. 1993). An international workshop have defined MSI as ‘a change of any length due to either insertion or deletion of repeating units, in a microsatellite within a tumour when compared to normal tissue’ (Boland et al. 1998). MSI-H (microsatellite instability – high) tumours are defined as having mutations in ≥ 2 of the five microsatellite sequences, MSI-L (microsatellite instability – low) as a mutation in 1 of the five microsatellite sequences and MSS (microsatellite stable) as having no mutations.

MSI testing is performed from the DNA extraction of lesions after fixation in formalin, and determines a deficiency of the MMR system (Tops et al. 2009). Immunohistochemistry (IHC) is then required to identify the specific defective MMR protein.

(3) CpG Island Methylator Phenotype (CIMP) Pathway:

CpG (Cytosine-phosphate-guanosine) islands are present in human genes in an unmethylated state (Armaghany 2012). The CIMP is characterised by methylation of multiple CpG islands, which results in down regulation of tumour suppressor gene function (Chan et al. 2002). This phenotype may be divided into two main types: CIMP-H, high level and CIMP-L, low level depending upon the degree of methylation.

Based upon the presence or absence of components of these pathways, Jass (2007) has suggested five colorectal cancer subtypes:

- (i) CIMP-high, methylation of MLH1, BRAF mutation, chromosomally stable, MSI-H – origin in serrated polyps.
- (ii) CIMP-high, partial methylation of MLH-1, BRAF mutation, chromosomally stable, MSS or MSI-L – origin in serrated polyps.
- (iii) CIMP-low, KRAS mutation, MGMT (0-6-Methylguanine DNA Methyltransferase) methylation, chromosomal instability, MSS or MSI-L – origin in adenomas or serrated polyps.
- (iv) CIMP-negative, chromosomal instability, mainly MSS – origin in adenomas (sporadic, Familial Adenomatous Polyposis (FAP) or MUTYH polyposis).
- (v) Lynch syndrome, CIMP-negative, BRAF mutation negative, chromosomally stable, MSI-H – origin in adenomas.

1.2.2 Histopathological Evidence For Colorectal Carcinogenesis

Muto et al. (1975) published a study from St Marks Hospital of 2506 colorectal polyps, some of which contained both benign and malignant components within the same polyp, providing evidence supporting the existence of a 'polyp-cancer sequence'. Based upon their data, they estimated that the polyp-cancer sequence occurred over an average of 10 – 15 years. However, this is likely to be dependant upon interplay between multiple environmental, hereditary and lesion factors. The authors of this paper also demonstrated that several factors including polyp size, villousness and degree of dysplasia were associated with an increased malignant potential of polyps, with polyp multiplicity identified as an additional risk factor for colorectal cancer (Muto et al. 1975). Supporting radiological evidence for the evolution of colonic polyps to colorectal cancer was published in a retrospective, pre - colonoscopy era study (Stryker et al. 1987). 226 patients with polyp's $\geq 10\text{mm}$ were followed up by serial barium enema examinations performed during the 1960's. 37% of polyps enlarged during the follow up period. The cumulative risk of colorectal cancer at the polyp site was calculated as 2.5% at 5 years, 8% at 10 years and 74% at 20 years. However this study was limited by its lack of inclusion of subcentrimetre polyps.

Following on from the work performed in St Marks hospital, the landmark National Polyp Study (NPS) from the USA examined over 3370 adenomatous polyps and demonstrated that several independent risk factors, including the in situ polyp size and extent of villous component, were associated with an increased risk of high grade dysplasia ($p < 0.0001$) (Muto et al. 1975; O'Brien et al. 1990). From this evidence the term 'advanced adenoma' has evolved and includes polyps with a villous architecture, $\geq 10\text{mm}$ and those with high grade dysplasia. Comparison of the adenoma prevalence from an autopsy series of 271 patients with the number of colorectal cancer cases within

a defined population, allowed an estimation of the annual conversion rate for all adenomas to colorectal cancer of 0.25%, for polyps ≥ 1 cm at $\sim 3\%$, villous adenomas at $\sim 17\%$ and those with severe dysplasia at $\sim 37\%$, supporting the notion of advanced adenomas being of higher risk (Eide 1986). These risk factors for high grade dysplasia are consistently reported throughout the literature (Gschwantler et al. 2002; Giuliana et al. 2006)

1.2.2.1 Polyp Type and Grade of Dysplasia

Irrespective of histological type, an increased risk of carcinoma is observed to develop in adenomas with an increasing grade of dysplasia (Muto et al. 1975). It has also been clearly demonstrated that the malignant potential of adenomas rises with increasing extent of villous component. The World Health Organisation (WHO) defines a villous adenoma as having at least an 80% villous component, tubulovillous at least a 20% villous component, with the remainder of lesions defined as tubular (Hamilton and Aaltonen 2000). Muto et al. (1975) documented this relationship, with cancer rates reported to rise from 4.8% in tubular adenomas, to 40.7% in villous adenomas. A similar trend was described in an analysis of over 5700 endoscopically resected adenomas (Shinya and Wolff 1979). The NPS also reported an odds ratio for high grade dysplasia of 20.2 in villous adenomas relative to tubular adenomas (O'Brien et al. 1990).

The severity of dysplasia and predominant villous component not only determine the malignant potential of a lesion, but also the risk of metachronous (recurrent) adenoma and carcinoma, forming part of the basis for surveillance. Atkin et al. (1992) followed up 1618 patients who had adenomas resected from the rectosigmoid colon during rigid sigmoidoscopy, over a mean period of 14 years. The authors reported a standardised incidence ratio (SIR) of 1.0 (95% CI 0.5 – 1.8) in tubular adenomas for the subsequent

risk of colon cancer, increasing to 5.0 (95% CI 2.2 – 9.9) for villous adenomas ($p = 0.0001$). A similar trend was observed with the grade of dysplasia, with mildly dysplastic adenomas having a SIR of 1.3 (95% CI 0.7 – 2.3), rising to 3.3 (95% CI 1.1 – 8.0) for severely dysplastic adenomas ($p = 0.01$). The more recent Veterans Affairs Cooperative Screening study reported a relative risk of colorectal cancer in patients with villous adenomas at 6.05, and those with high grade dysplasia at 6.87 (Lieberman et al. 2007).

1.2.2.2 Polyp Size

An increased risk of carcinoma is observed with increasing polyp size, irrespective of histological type (Muto et al. 1975). The NPS showed that compared with small (≤ 5 mm) adenomas, the odds ratio for high grade dysplasia in polyps 6 – 10mm is reported at 4.8, rising significantly to 20.7 for adenomas > 10 mm (O'Brien et al. 1990).

A sigmoidoscopy trial also demonstrated polyp size to be a risk factor for colon cancer (Atkin et al. 1992). For adenomas < 10 mm the SIR for colon cancer was 1.5 (95% CI 0.8 – 2.4), increasing to 2.2 (95% CI 1.1 – 4.0) for polyps of 1 – 2 cm and 5.9 (95% CI 2.8 – 10.6) for polyps > 2 cm ($p = 0.002$). Several other studies have confirmed these findings (Yang et al. 1998; Bertario et al. 2003; Lieberman et al. 2007).

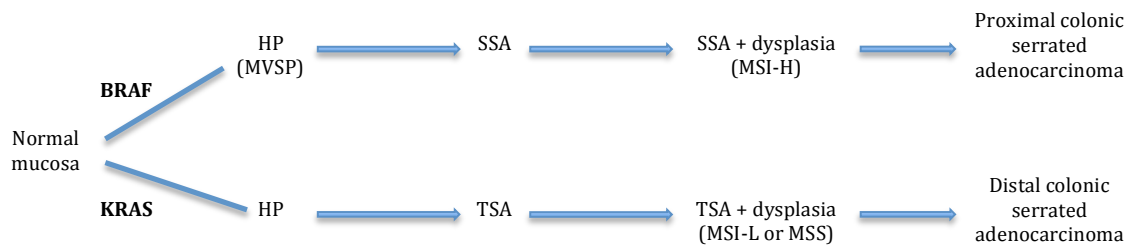
1.2.2.3 Polyp Multiplicity

It has long been recognised that colorectal cancer risk correlates to the number of adenomas present in the colon. Muto et al. (1975) reported the risk of colorectal cancer in individuals with one adenoma at 22%, rising to 69% in individuals with ≥ 6 adenomas. Data from the NPS reported 7.3% of patients with one adenoma had high grade dysplasia, rising to 20% in those with ≥ 5 adenomas (O'Brien et al. 1990). Several

studies and a meta – analysis have also reported an increased risk of advanced adenomas during follow up surveillance procedures in patients with a higher number of adenomas at baseline (van Stolk et al. 1998; Noshirwani et al. 2000; Saini et al. 2006; Lieberman et al. 2007). A prospective colonoscopy study reported the relative risk (RR) for recurrence of advanced adenomas at 5.01 in patients with ≤ 2 subcentimetre tubular adenomas at baseline, compared with a RR of 6.40 for those with ≥ 3 subcentimetre tubular adenomas (Lieberman et al. 2007). The relationship between polyp number and risk of colorectal cancer is also demonstrated by several Mendelian inheritance syndromes such as Familial Adenomatous Polyposis (FAP) and MUTYH-associated polyposis (MAP), where the presence of hundreds to thousands of adenomas is associated with the inevitable development of colorectal cancer (Burt et al. 2004; Farrington et al. 2005).

1.2.3 Serrated Pathway

Compared to the adenoma-carcinoma pathway, the progression of serrated polyps to adenocarcinoma has only recently been described and is thought to incorporate two serrated pathways (Figure 3), characterised by either BRAF or K-ras mutations (Torlakovic and Snover 1996; Huang et al. 2011). BRAF forms a protein named B-Raf, which is a member of the RAF family. Mutation of BRAF results in cell proliferation and inhibition of apoptosis (Leggett and Whitehall 2010). It is now acknowledged that serrated polyps progressing down the serrated pathway may explain the reason why resection of conventional adenomas, typically located in the distal colon does not protect against proximal colonic cancer.



HP, Hyperplastic polyp; **MSI**, Microsatellite Instability; **MSI-H**, Microsatellite Instability High; **MSI-L**, Microsatellite Instability Low; **MSS**, Microsatellite Stable; **MVSP**, Microvesicular Serrated Polyp; **SSA**, Sessile Serrated Adenoma; **TSA**, Traditional Serrated Adenoma.

Figure 3 Serrated pathway (Adapted from Noffsinger 2009; Huang et al. 2011).

The World Health Organisation has defined three main types of serrated polyps including hyperplastic polyps (HP), sessile serrated adenomas (SSA) and traditional serrated adenomas (TSA) (Snover et al. 2010). Hyperplastic polyps account for 80 – 90% of all serrated polyps, but are usually diminutive ($\leq 5\text{mm}$) and located in the distal colon, where they are thought to be of no clinical significance (Makinen 2007). HPs may be further subdivided into goblet cell serrated polyps (GCSP) and microvesicular serrated polyps (MVSP). MVSPs are more likely to contain BRAF mutations and have a propensity to progress to SSAs, especially in the right colon. This compares to GCSPs, which are more likely to contain K-ras mutations.

SSA's may occur without dysplasia (also termed sessile serrated polyps or sessile serrated lesions) or with dysplasia. They are estimated to account for up to 9% of all polyps (Huang et al. 2011). SSA's are more common in the proximal colon, where they are also significantly larger than in the distal colon (Messick et al. 2012). They are characterised by BRAF mutations and high levels of CpG island methylation phenotype (CIMP-H) (Huang et al. 2011). In a study of 2139 patients with SSA's, 2% were identified to contain high grade dysplasia and 1% adenocarcinoma (Lash et al. 2008).

TSA's are similar to conventional adenomas both in their histological appearance and distal location within the colon (Noffsinger 2009). In comparison to SSA's with dysplasia, K-ras mutations predominate in TSA's (Huang et al. 2011). However K-ras mutations still occur less frequently in serrated than conventional adenomas (Ajioka et al. 1998).

Serrated adenocarcinoma is estimated to form 7.5% of all colorectal cancers and is more commonly identified in women (Tuppurainen et al. 2005). Around 55% of serrated adenocarcinomas are microsatellite-stable, however MSI-L is significantly more common in serrated than non-serrated cancers (Tuppurainen et al. 2005). Whilst serrated polyp surveillance recommendations have been proposed by an international expert panel, due to the current paucity of published data regarding outcomes following endoscopic resection of these lesions, surveillance is commonly performed as for conventional adenomas (Rex et al. 2012). It is recognised that identification of serrated lesions at colonoscopy can be challenging. The presence of mucous caps, a rim of debris or interruption of the contour of a fold should alert the endoscopist to the possibility of an underlying serrated lesion (Tadepalli et al. 2011).

1.2.4 Polyp Morphology

Whilst polyp morphology was initially broadly categorised as polypoidal or non-polypoidal, their description has since been refined. The Paris classification was established by an international group of endoscopists, surgeons and pathologists with the aim of standardising the terminology for polyp morphology worldwide (Participants in the Paris Workshop 2003). Using the Paris classification, superficial lesions are described as subtypes of "type 0" (Figure 4). Within type 0, there are two main subtypes: (i) polypoid: includes Ip (pedunculated) and Is (sessile) lesions (ii) non –

polypoid: includes IIa (flat elevated), IIb (flat), IIc (slightly depressed) and III (excavated) (Figures 5 – 8). Some lesions may incorporate several different morphologies, described using combinations of this classification (e.g: 0-IIaIIc).

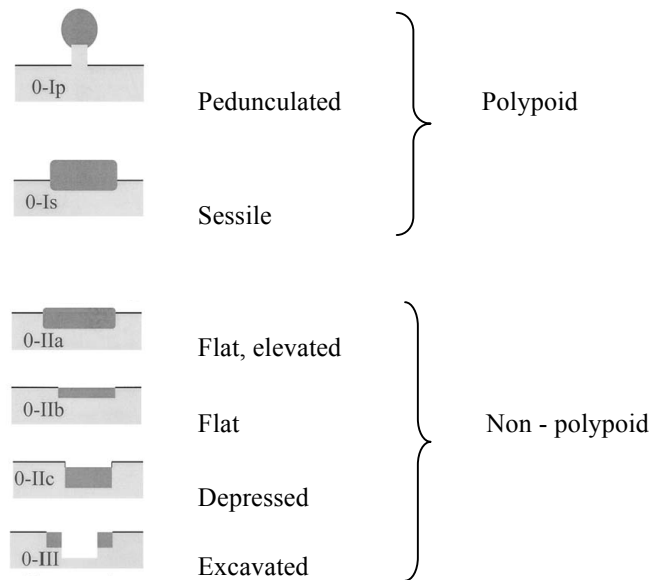


Figure 4 Paris Classification (Adapted from Participants in the Paris Workshop 2003)



Figure 5 Pedunculated (0-Ip) lesion



Figure 6 Subpedunculated (0-Ips) lesion



Figure 7 Sessile (0-Is) lesion

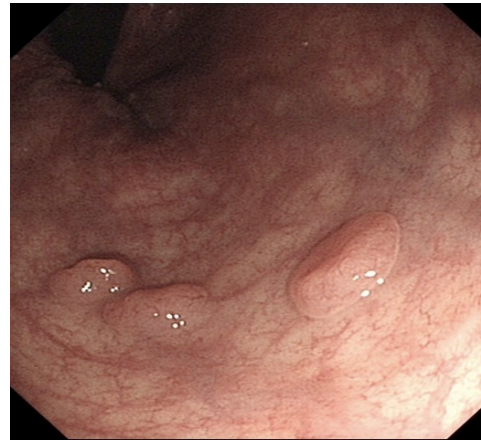


Figure 8 Flat elevated (0-IIa) lesions

1.2.4.1 Flat Lesions

Flat polyps were first described in the 1970's and later defined as having 'a flat or rounded surface combined with a height of less than one half its diameter' (Muto et al 1975; Muto et al. 1983). The overall incidence of flat adenomas in patients undergoing colonoscopy is reported at 8 – 40% (Speake et al. 2007). They more commonly arise in the right colon, with higher rates of high grade dysplasia (43%) compared with polypoidal lesions (12%), and evidence of low grade dysplasia identified in up to 86% of flat lesions (Jaramillo et al. 1995; Speake et al. 2007; Park et al. 2008a). Higher rates of adenocarcinoma are consistently reported when compared with polypoidal lesions, which is significantly higher in depressed lesions (Paris classification 0-IIc) (Rembacken et al. 2000; Hurlstone et al. 2003; Speake et al. 2007; Park et al. 2008a; Matsuda et al. 2010). Whilst K - ras mutations are identified less frequently than in polypoidal lesions, MSI instability is more common (Kaneko et al. 1998; Ogawa et al. 2006; Speake et al. 2007).

1.3 Rationale For Colonoscopic Screening And Surveillance

The rationale for polyp surveillance and development of both national and international guidelines has evolved from several pieces of evidence: (i) a reduction in the risk of colorectal cancer following polypectomy, based upon epidemiological evidence, (ii) the detection rate of further adenomas at follow up after clearance colonoscopy and (iii) the documented miss rates and variance in adenoma detection rates between colonoscopists. Whilst size, morphology and histology help determine a polyps malignant potential, there is currently no method to establish which lesions will progress to adenocarcinoma. It is therefore recommended that all neoplastic lesions should be resected, unless an individual's comorbidity determines otherwise.

1.3.1 Evidence For Polyp Progression And Regression

Evidence for polyp progression to carcinoma was initially demonstrated through serial barium enema examinations of untreated colonic polyps ≥ 1 cm in size (Stryker et al. 1987). The cumulative risk of cancer at the polyp site increased from 2.5% at five years to 24% at twenty year follow up. Since the advent of colonoscopy, several studies have reported on the natural history of subcentimetre polyps. Hofstad et al. (1994 and 1996) published serial papers from a study following subcentimetre polyps in 116 patients, over a one and three year period. The polyp position was photographed and location documented as the distance of the straight colonoscope from the anus. Polyp size was measured in situ using a graded endoscopic probe, passed down the accessory channel of the colonoscope. Follow up colonoscopy was performed by the same endoscopist after one year (Hofstad et al. 1994). The authors reported polyps < 5 mm to have significantly increased in size ($p = 0.05$), compared with polyps of 5 – 9mm that had significantly reduced in size ($p = 0.04$). However the overall polyp sizes were not significantly different. Further results were published by the authors two years later

(Hofstad et al. 1996). Over the entire three year study period, 25% of adenomas remained the same size, 40% grew larger and 35% had shrunk or regressed in size. The main limitation of this study was the potential inability to accurately identify the same individual polyp for follow up measurements. Further evidence of polyp regression has also been provided from re – analysis of data from the National Polyp Study (Loeve et al. 2004b). Recent molecular genetic studies suggest that adenoma progression may be episodic, with periods of quiescence interspersed by rapid clonal expansion, demonstrating the progression of adenomas to carcinoma to be non-linear (Humphries et al. 2012).

1.3.2 Effect of Polypectomy on Colorectal Cancer Risk

As early as 1974 it was shown that removal of left sided adenomatous polyps could reduce the incidence of colorectal cancer (Gilbertsen 1974). Gilbertsen reported results of a 25 year follow up study involving over 18,000 patients undergoing annual sigmoidoscopy. The incidence of rectal cancer was 85% lower than anticipated by statistical analysis (Gilbertsen and Nelms 1978). A reduction in the risk of distal colonic and rectal cancer has also been observed in more recent sigmoidoscopy trials (Atkin et al. 1992; Selby et al. 1992; Muller and Sonnenberg 1995). The impact of sigmoidoscopy screening in individuals aged 55 – 64 years old has also been evaluated in a randomised controlled trial of over 170,000 participants (Atkin et al. 2010). The incidence of rectosigmoid cancer was reduced by 50%, with a 33% reduction in colorectal cancer overall in the screened group.

The impact of colonoscopic surveillance was reported in the landmark American National Polyp Study (NPS), published in 1993 (Winawer et al. 1993b). 1418 patients were recruited prospectively and underwent baseline colonoscopy and removal of

adenomatous polyps, with follow up colonoscopy performed at three then six years. The incidence of colorectal cancer in this group, with an average follow up interval of 5.9 years, was compared to three large cohorts of data from the Mayo clinic, St Marks Hospital in London and American Surveillance, Epidemiology and End Results (SEER) data. The incidence of colorectal cancer post - polypectomy was significantly reduced, by up to 90% compared to the reference populations ($p < 0.001$). Further studies from Italy and Norway have demonstrated similar findings (Thiis-Evensen et al. 1999; Citarda et al. 2001). Citarda et al. (2001) performed a retrospective review of 1693 patients undergoing resection of adenomas $> 5\text{mm}$, with a mean follow up interval of 10.5 years. The number of observed cancers was compared with the number of expected cancers, calculated using data correlated from Italian cancer registries. The overall incidence ratio was reported at 0.34 ($p < 0.01$), indicating a lower than expected number of cases of colorectal cancer post - polypectomy. The Norwegian Telemark study compared a screening group of 400 patients who underwent resection of polyps $\geq 5\text{mm}$, with a control group of 399 individuals (Thiis-Evensen et al. 1999). The relative risk of colorectal cancer was reported at 0.2 ($p < 0.02$). Loeve et al. (2004a) studied the effect of adenoma resection upon colorectal cancer risk in 78,473 patients and reported a decrease in the incidence ratio from 2.8 in year two of follow up to 0.9 in years nine to eleven, converse findings to those expected. The authors hypothesised that their high incidence of reported colorectal cancer in years one to five post – polypectomy was due to missed cancers at the index procedure.

1.3.3 Rationale For Post Polypectomy Surveillance

The rationale for post polypectomy surveillance colonoscopy is based upon several factors. Foremost, the evidence derived from several studies that have reported the detection rates of adenomas following clearance colonoscopy at up to 42% during

follow up procedures performed within 1 – 3 years, and even higher in patients with multiple adenomas (Waye and Braunfeld 1982; Winawer et al. 1993a; Jorgensen et al. 1995; Neugut et al. 1995). This may in part be secondary to adenoma miss rates and adenoma detection rates, which can vary significantly between endoscopists (Imperiale et al. 2009). The Funen Adenoma follow up study included 673 patients randomised to surveillance colonoscopy after two or four years (Jorgensen et al. 1995). The cumulative risk of adenomas was 35.0% in the two year surveillance group and 35.5% in the four year group. Another study randomised 1418 patients to colonoscopic surveillance at one and three year intervals or three years only (Winawer et al. 1993b). Whilst the percentage of adenomas detected was significantly higher with closer surveillance (41.7% verses 32%, $p = 0.006$), there was no significant difference identified in the number of advanced adenomas detected. Despite surveillance, patients may present with interval cancers thought to develop from missed or rapidly growing lesions (Makinen 2007).

1.3.4 Polyp Miss Rates

The detection of adenomas at follow up colonoscopy may in part be due to the inherent miss rates secondary to factors such as bowel preparation and withdrawal technique (discussed in section 1.6). Several studies have aimed to quantify this. One of the first trials recruited 183 patients who underwent same day back to back colonoscopy by the same or different colonoscopist (Rex et al. 1997). The overall miss rate for adenomas was 24%, ranging from 27% for adenomas ≤ 5 mm to 6% for those ≥ 1 cm. These findings have been consistent throughout several studies, with increasing miss rates associated with smaller polyp sizes (Hixson et al. 1991; Postic et al. 2002; Harrison et al. 2004). A systematic review of 465 patients reported an overall polyp miss rate of

22% (van Rijn et al. 2006). The miss rate for adenomas 1 – 5mm was 26%, 13% for 5 – 10mm and 2.1% for polyp's \geq 10mm.

1.3.5 Adenoma Detection Rates (ADRs)

Adenoma detection rates have been reported to vary significantly between endoscopists. A study of 25 endoscopists performing over 2600 colonoscopies reported ADRs ranging from 7 – 44% ($p < 0.001$) (Imperiale et al. 2009). Additional studies have demonstrated a similar variance (Bretthauer et al. 2003; Chen and Rex 2007; Millan et al. 2008). Several factors may influence this variation, including examination of the proximal aspects of the flexures and folds, adequate bowel cleaning, suctioning and distension, and the time spent viewing the mucosal surface (Rex 2000). The importance of colonoscopic technique was highlighted by the results of a prospective multi - centre trial studying the location of adenomas missed by colonoscopy in 1233 patients who underwent same day virtual colonoscopy (Pickhardt et al. 2004). The majority of missed adenomas were located on a fold (93.3%), usually on its oral (cranial facing) aspect (71.4%).

Similar differences in ADR's have been reported for sigmoidoscopy procedures (Bretthauer et al. 2003; Atkin et al. 2004). Adenoma detection rates were studied in 13 endoscopists, as part of a UK flexible sigmoidoscopy screening trial and varied between 10.4 to 21.7 per 100 cases (Atkin et al. 2004).

Current UK guidance recommends a minimum standard of adenoma detection rate of \geq 15%, although following a recent national colonoscopy audit reporting an overall polyp detection rate of 32.1%; this cut off is likely to be reviewed in the future (Gavin et al. 2013).

1.3.6 Adenoma Prevalence Rates

Several autopsy series have studied the prevalence of adenomas in relation to patient age. All have demonstrated increasing prevalence with age, peaking in the age range 60 – 80 years old (Table 1). The age at which screening and surveillance programmes commence is largely based around this data.

Age (years)	Percentage of patients with adenomas at autopsy (%)				
	Stemmermann and Yatani 1973	Sato et al. 1976		Vatn and Stalsberg 1982	Coode et al. 1985
		Akita	Miyagi		
20 - 29	/	12.5	5.9	/	/
30 – 39	/	16.7	17.6	/	/
40 – 49	/	11.1	21.1	/	/
50 – 59	52.0	26.8	19.2	23.0	19.4
60 – 69	59.3	44.0	26.3	31.0	31.0
70 – 79	61.8	40.4	32.8	44.0	43.9
80+	64.8	41.7	43.8	47.0	27.3

Table 1 Adenoma prevalence rates according to age

1.4 Colorectal Cancer Risk Groups

An individual’s risk of developing colorectal cancer may be stratified according to a combination of their family history and molecular genetic studies, into one of three risk groups: average, moderate or high (Cairns et al. 2010). The definition, surveillance recommendations and long term management of each of these groups varies both nationally and internationally (Cancer Genetics Service for Wales 2006; Davila et al. 2006; Vasen et al. 2008; Cairns et al. 2010). Overall 15 – 30% of colorectal cancers are estimated to be secondary to a genetic predisposition (15% in moderate risk group and around 2 – 5% due to autosomal dominant or recessive inherited syndromes) (Dove-Edwin and Thomas 2001; Tops et al. 2009).

1.4.1 Average Risk Group

An average risk individual is defined as one who has the same or similar lifetime risk of developing colorectal cancer as the general population. The lifetime risk of colorectal cancer in the United Kingdom is approximately 1 in 15 for men and 1 in 19 for women (Cancer Research UK 2012). Until recently this group underwent no intervention unless symptomatic. In July 2006 Bowel Cancer Screening was introduced in England and later commenced in Wales in October 2008. It involves population based screening for colorectal cancer using Guaiac faecal occult blood (FOB) testing. Participants with equivocal test results receive an immunochemical kit. This programme has been introduced in a phased approach, initially targeting those aged 60 – 69 years old, with gradual expansion to ultimately include those aged between 50 – 74 years old across the UK. Those with negative results are recalled for further screening two years later. In the case of positive FOB results, individuals are invited to attend for screening colonoscopy unless their comorbidity determines otherwise, in which case CT pneumocolon may be performed as an alternative.

1.4.2 High Risk Groups

1.4.2.1 Familial Adenomatous Polyposis (FAP)

FAP is an autosomal dominant inherited condition, resulting from a mutation of the tumour suppressor ‘adenomatous polyposis coli’ (APC) gene, located on chromosome 5q, and accounts for < 1% of colorectal cancers (Burt et al. 1990). It results in 100’s – 1000’s of colorectal adenomas. Gastric and duodenal adenomas are also a feature of this disease, as well as extraintestinal malignancies including desmoid tumours, thyroid cancer and hepatoblastomas (Galiatsatos and Foulkes 2006). Attenuated FAP (AFAP) is a variant of FAP, resulting in fewer than 100 adenomas but is still associated with a significantly higher cancer risk. Colorectal cancer predominates in the distal colon in

FAP (76%), which is the converse of AFAP where most cancers are identified in the proximal colon (75%) (Bjork et al. 1999; Burt et al. 2004).

1.4.2.2 Hereditary Non - Polyposis Colorectal Cancer (HNPCC)

HNPCC, also termed Lynch syndrome, has an autosomal dominant inheritance and accounts for 1 – 3% of colorectal cancers (Lynch and de la Chapelle 2003). It occurs due to mutations in mismatch repair genes including MLH1, MSH2, MSH3, MSH6, PMS1 and PMS2 (Fishel et al. 1993; Nicolaidis et al. 1994; Papadopoulos et al. 1994; Lynch and de la Chapelle 2003). These genes normally repair errors occurring during DNA replication. Several clinical criteria have been developed and modified to identify those individuals appropriate for genetic testing, including the Amsterdam II and Bethesda criteria. The Bethesda criteria identify those individuals suitable for MSI testing. Microsatellite instability and immunohistochemistry testing are undertaken initially. Those with abnormal results undergo germline testing to look for mutations in these genes (Vasen et al. 2007).

Polyps predominantly arise in the right colon (Lynch et al. 1985a), and progress through the adenoma – carcinoma sequence over a 2 – 3 year period, much shorter than for sporadic cancer (Grover and Syngal 2009). Patients have an 80% lifetime risk of colorectal cancer, diagnosed at an average age of 44 years old (Burt and Neklason 2005). Cancers also are predominantly located in the right colon, proximal to the splenic flexure (76%) (Cao et al. 2002; Mecklin et al. 2007).

1.4.2.3 Human MutY homologue (MUTYH) – Associated Polyposis (MAP)

Compared with the other high risk cancer genetic syndromes, MAP was only recently described in 2002 (Al-Tassan et al. 2002). It follows an autosomal recessive inheritance pattern and accounts for approximately 1% of colorectal cancers (Tops et al. 2009). The prevalence of the MAP defect in the population is presently unknown (Sampson and Jones 2009). A deficiency in the base excision repair of DNA results from MUTYH (Human MutY homologue) gene mutations, preventing repair of mutations resulting from oxidative DNA damage. This cohort of patients most frequently present with colorectal adenomas at a mean age of 45 years old and with colorectal cancer at a mean age of 48 years old (Nielson et al. 2009). Some mutations confer a 93 fold increased risk of colorectal cancer (Farrington et al. 2005). The number of adenomas and hyperplastic polyps may vary from less than ten to several hundred, making it phenotypically similar to FAP or AFAP in some cases (Sampson et al. 2003; Chow et al. 2006). Hence genetic testing for the MUTYH mutation is advised in patients with multiple colorectal adenomas if an APC mutation is not identified. In a study of 254 patients identified with MAP, 33% of those who developed colorectal cancer had a metachronous or synchronous tumour (Nielson et al. 2009). The majority (56%) of cancers were identified proximal to the splenic flexure. This distribution is similar to locally reported data, where over 20% of cancers were identified in the rectosigmoid colon (Jones 2007). Serrated polyps have been reported to be present in up to 47% of patients, with 18% of these meeting the diagnostic criteria for Serrated Polyposis Syndrome (Boparai et al. 2008).

1.4.2.4 Serrated Polyposis Syndrome

Formerly known as Hyperplastic Polyposis Syndrome, this condition was renamed Serrated Polyposis Syndrome (SPS) by the World Health Organisation (WHO) in 2010 (Snover et al. 2010). It is defined by the WHO as: (1) at least five histologically diagnosed serrated polyps proximal to the sigmoid colon of which two are $\geq 10\text{mm}$ or (2) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first degree relative with SPS or (3) > 20 serrated polyps of any size, but distributed throughout the colon (Snover et al. 2010). The majority of patients have polyps located throughout the large bowel (89%), with 7% predominantly in the proximal colon and 4% predominantly in the distal colon (Rosty et al. 2012). Whilst a genetic inheritance pattern has not been identified, up to 50% of patients report a first degree relative with colorectal cancer (Chow et al. 2006). Due to this, screening is advocated for first degree relatives of patients with SPS (Lage et al. 2004; Guarinos et al. 2012). BRAF mutations and CIMP high hyperplastic polyps occur with large, multiple or right colonic hyperplastic polyps, where there is absence of K - ras (Chan et al. 2002; Beach et al. 2005).

SPS is associated with an increased risk of colorectal cancer of around 25 – 40% (Rosty et al. 2012). This may in part be due to the presence of co-existing serrated or conventional adenomas, with the presence of ≥ 1 conventional adenomas associated with colorectal cancer ($p = 0.03$) (Rashid et al. 2000; Rosty et al. 2012). Cancers occurring in SPS may be MSI - H, MSI - L or MSS (Jass et al. 2000; Leggett et al. 2001).

1.4.3 Moderate Risk Group

The moderate risk group represents a cohort of patients who do not follow a specific Mendelian inheritance pattern, but have an increased risk of colorectal cancer above the general population. Diagnosis is based upon an individual's family history of colorectal cancer rather than molecular genetic studies, although work from genome wide association studies is starting to provide a further understanding of the pathways leading to colorectal cancer in these individuals (Tenesa and Dunlop 2009). After exclusion of high risk patient groups, recent studies have demonstrated an association between an increased number of risk alleles on identified loci and odds of having a familial colorectal cancer. (Niittymaki et al. 2010; Dunlop et al. 2012). In addition, dietary and metabolic factors such as the consumption of red meat also seem to play a role (Benamouzig and Uzzan 2011). An individual's risk of colorectal cancer consistently increases with the number of first degree relatives affected and the younger the age of the relative (St John et al. 1993; Fuchs et al. 1994; Butterworth et al. 2006).

Both a paucity and heterogeneity in published data has lead to variance in the definition and surveillance recommendations for this group amongst international societies (Table 2). Current national (UK) guidelines broadly divide this group into low-moderate risk individuals, who have a slight increased risk of colorectal cancer above the general population leading to the recommendation of a single colonoscopy aged 55 years old; and the high-moderate risk group who either have negative molecular genetic studies or whom do not fulfil diagnostic criteria for the high risk group (Cairns et al. 2010). Surveillance colonoscopy is recommended every 5 years commencing at the age of 50 years old up until the age of 75 in this latter group, unless pathology identified during the procedure determines otherwise (Table 2). The aim of surveillance is for the detection and removal of conventional adenomas and serrated polyps, thereby

interrupting the relevant cancer pathways with the aim of reducing the risk of colorectal cancer. Local guidelines published by the Cancer Genetics Service for Wales currently differ slightly from national guidelines in their surveillance recommendations, with advice to commence 5 yearly colonoscopic surveillance in high-moderate risk individuals, 5 years prior to the youngest diagnosis of colorectal cancer in a relative, taking into account the pathways outlined above (Cancer Genetics Service for Wales 2006) (Table 2). There are currently few publications reporting the yield of surveillance colonoscopy in this patient group (Bradshaw et al. 2003; Clark et al. 2003; Mak et al. 2007).

Criteria	Surveillance recommendations
Cancer Genetics Service for Wales referral guidelines for individuals with a family history of colorectal cancer (2006)	
<ul style="list-style-type: none"> • One FDR diagnosed \leq 45 years old • Two FDRs (including both parents) or one FDR and one SDR on the same side of the family diagnosed at any age • Three relatives all on the same side of the family (at least one a FDR) 	Usually 5 yearly, starting from when the individual is 5 years younger than the youngest diagnosis of CRC in the family (Chapter 4)
Previous British Society of Gastroenterology guidelines (Dunlop 2002)	
<ul style="list-style-type: none"> • One FDR affected by CRC < 45 years old • Two affected FDRs 	At consultation or between age 35-40 years old (whichever is later) and repeat procedure at 55 years old
Updated British Society of Gastroenterology guidelines (Cairns et al. 2010)	
<u>High-moderate risk group</u> <ul style="list-style-type: none"> • CRC in three FDRs in 1st degree kinship* (none < 50 years) • CRC in two FDR in 1st kinship* (mean age 60 years old) 	5 yearly colonoscopy from age 50 to 75 years old
<u>Low-moderate risk group</u> <ul style="list-style-type: none"> • CRC in two FDR \geq 60 years old • CRC in one FDR < 50 years old 	Single colonoscopy at age 55 years old. No follow up if normal
American Society Gastrointestinal Endoscopy guidelines (Davila et al. 2006)	
<ul style="list-style-type: none"> • FDR with CRC < 60 years old 	3 – 5 yearly colonoscopy from age 40 or 10 years younger than the affected relative (whichever is younger)
<ul style="list-style-type: none"> • FDR with CRC age \geq 60 years 	10 yearly colonoscopy from age 40
National Health & Medical Research Council guidelines – Australian government (2005)	
<ul style="list-style-type: none"> • One FDR with CRC < 55 years old • Two FDR or SDR on the same side of the family with CRC diagnosed at any age 	5 yearly colonoscopy from age 50 or 10 years younger than the affected relative (whichever is younger)

CRC, colorectal cancer; **FDR**, first degree relative; **SDR**, second degree relative

*Affected relatives are FDRs of each other and at least one is a FDR of the patient.

Table 2 Local, national and international referral and surveillance guidelines for patients with a moderate family history risk of colorectal cancer (these guidelines provide surveillance recommendations in the context of a normal colonoscopy)

1.5 Medical and molecular genetics in the management of moderate risk groups.

The Medical Genetics service has numerous roles including confirmation of a reported family history using a variety of resources, to provide an accurate risk assessment and stratification of an individual's risk of colorectal cancer. It also provides the counselling of patients and where appropriate their relatives and genetic testing in the context of familial cancers. It is important to ensure that accurate risk assessment is undertaken, as under reporting of a family history can lead to missed opportunity for surveillance, whereas over reporting may expose an individual to the unnecessary risks of colonoscopy in the context of colorectal cancer.

Individuals with a family history of colorectal cancer follow numerous pathways through primary and secondary care services. The pathway taken may be influenced by the presence or absence of symptoms in the individual. Symptomatic patients are commonly referred to gastroenterologists or colorectal surgeons for colonic investigation and then referred to the Medical Genetics department at a later stage for formal risk stratification. The converse is often true for asymptomatic individuals who may initially be referred to medical genetics for risk stratification and depending upon the advice provided, later referred for colonoscopic surveillance. However service structures vary both nationally and internationally (Hodgson et al. 1999; Wonderling et al. 2001).

1.5.1 Accuracy of Data Collection

During data collection there appears to be no difference in the accuracy of information provided to genetic services whether obtained in a written format or at interview (Kelly et al. 2007). The reporting of a family history varies with several factors including the

degree of relationship to the proband and the type of malignancy, being less accurate for colorectal compared with breast cancer (Douglas et al. 1999; Sijmons et al. 2000). It is unaffected by the age, gender or college education of the individual (Kerber and Slattery 1997; Douglas et al. 1999; Sijmons et al. 2000). The variance between reported and confirmed information provided can potentially alter management in up to 11% of cases (Douglas et al. 1999; Sijmons et al. 2000).

Despite counselling, approximately 50% of individuals still under or over estimate their risk of colorectal cancer and this seems unaffected by whether they are reviewed in clinic (Liljegren et al. 2004; Holloway et al. 2005).

1.5.2 Surveillance Compliance

A Swedish postal survey reported 80% of patients undergoing colonoscopy for a family history of colorectal cancer to understand the rationale for surveillance, with a high perceived benefit (Liljegren et al. 2004). However the compliance rates for colonoscopy in first degree relatives of patients with advanced colorectal adenomas or cancer range from 18 – 38% and are higher in relatives aged < 65 years old and in siblings and offspring compared with parents (Cottet et al. 2006; Bujanda et al. 2007).

1.6 Endoscopic Optimisation of Polyp Detection

The principal goal of any screening or surveillance procedure is to ensure adequate detection and resection or treatment of relevant colorectal pathology. Colonoscopy is the current gold standard modality acting as a diagnostic tool, in addition to allowing therapeutic interventions such as polypectomy to be undertaken.

Several endoscopic techniques and technologies have been evaluated in their role of optimising lesion detection.

1.6.1 Chromoendoscopy (Dye spray)

The initial use of dye spray was described in the stomach (Yamakawa et al. 1966). Tada et al. (1977) later described its use within the colon. Chromoendoscopy has evolved three principal roles: (1) lesion detection: it may be used during screening or surveillance procedures to improve polyp detection, (2) lesion assessment: to distinguish non – neoplastic from neoplastic lesions using surface pit pattern recognition and (3) demarcation of lesions: to define the margin of lesions so that their extent can be delineated and decisions made regarding endoscopic resection.

Methylene blue and indigo carmine are the two principal dyes used in the detection of colorectal lesions (Shim 1999). Methylene blue is classified as an absorptive (vital) stain, which is actively absorbed into the colonic epithelial cells, staining them blue. The absence or altered dye uptake indicates abnormal mucosa. Concerns have been raised with use of this dye and its potential to cause DNA damage to colonocyte cells in vitro and in vivo, and resulting carcinogenic effect (Davies et al. 2007). However there is no published clinical evidence of increased malignant risk (Dinis-Ribeiro and Moreira-Dias 2008). Indigo carmine, a contrast (reactive) stain, combines a blue plant dye (indigo) and a red colouring (carmine) (Fennerty 1994). This dye collects between the epithelial cells in the pits and grooves of the mucosal surface, but is not absorbed (Canto 1999).

For lesion detection, each colonic segment is examined systematically using a dye after removing any pools of fluid or stool. The dye is most commonly applied through a plastic spray catheter that is passed through the accessory channel of the colonoscope, until it is just visible in the lumen. The endoscopy assistant injects a continuous stream of dye through the catheter, during a spiral withdrawal of the colonoscope within a

determined segment of bowel by the endoscopist (Wong Kee Song et al. 2007). The lumen of the colon is collapsed by aspiration of the air or carbon dioxide gas used to inflate the bowel, resulting in an even coating of the mucosal surface with dye. The colon is then insufflated, with any excess pools of dye aspirated, so that a methodical review of the mucosal surface may be undertaken for lesion detection (Figure 9). This process is repeated for each segment of bowel, until the length of the colon is examined. Good bowel preparation is required for chromoendoscopy to be effective. The main disadvantages of chromoendoscopy are its need for additional equipment and associated costs, as well as the increased time required for application and examination. Whilst uncommon, adverse reactions to the dyes have also been reported (Shim 1999).

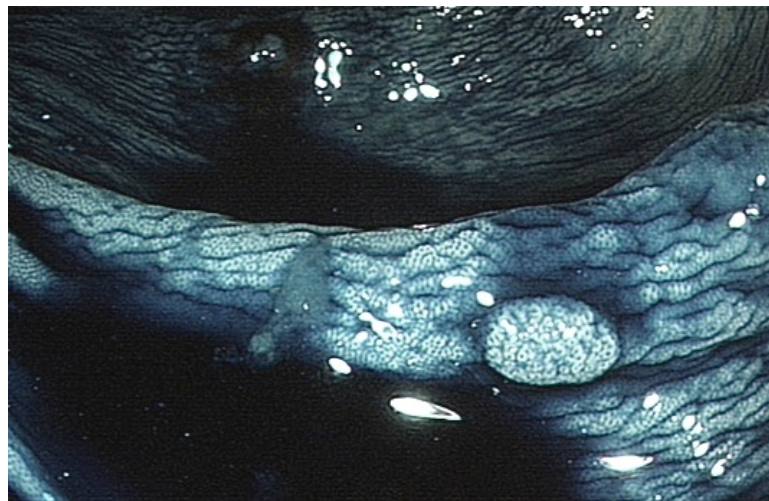


Figure 9 Diminutive polyp detected during pancolonoscopic chromoendoscopy using indigo carmine dye

Brooker et al. (2002) were one of the first groups to study the impact of panchromoendoscopy upon polyp detection rates in the colon. 259 patients were randomised between dye spray with 0.1% indigo carmine or standard white light withdrawal. A longer median time period was taken for withdrawal in the dye spray compared to control group; 9:05 minutes versus 4:52 minutes ($p < 0.0001$).

Chromoendoscopy significantly increased the number of diminutive ($\leq 5\text{mm}$) lesions, both non – neoplastic and neoplastic. However it should be noted that a minimum colonoscope withdrawal time of 6 minutes has since been established as a quality indicator (Chilton and Rutter 2011). It was uncertain from this study whether the variation in withdrawal times may have influenced the polyp detection rates. Hurlstone et al. (2004) took this into consideration during a similarly designed randomised trial of 260 patients using 0.5% indigo carmine dye. There was no notable difference in the median withdrawal times in the chromoendoscopy group (17 minutes) compared with control group (15 minutes) ($p > 0.1$). However the findings were similar to the previous study, with significantly more adenomas identified in the dye spray versus control group (66% versus 33%; $p < 0.05$). A higher number of flat and diminutive polyps were also detected in the chromoendoscopy group, especially in the right hemicolon ($p < 0.05$). Four further studies looking at panchromoendoscopy have reported similar findings, as well as the use of chromoendoscopy specifically in the ascending colon and caecum (Stergiou et al. 2006; Park et al. 2008b; Stoffel et al. 2008; Pohl et al. 2011). However Le Rhun et al. (2006) reported no significant difference in the total number of adenomas per patient, but a significantly higher number of flat adenomas in the chromoendoscopy group. When the distal colon alone is examined by chromoendoscopy, whilst the number of flat diminutive polyps detected is increased, there is no significant increase in the number of patients with adenomas detected compared with controls (Lee et al. 2003; Ratiu et al. 2007; Hashimoto et al. 2010). A Cochrane review of chromoendoscopy excluding patients with polyposis syndromes and inflammatory bowel disease summarised that chromoendoscopy identifies more patients with at least one adenoma (OR – 1.61) and significantly more patients with ≥ 3 neoplastic lesions (OR – 2.55) (Brown et al. 2007). However this needs to be balanced against the resource implications such as an increased procedure time and equipment costs.

Chromoendoscopy has also been appraised in patients at high risk of colorectal cancer. A single study of thirteen patients with Familial Adenomatous Polyposis, compared white light colonoscopy with narrow band imaging, autofluorescence imaging and chromoendoscopy with indigo carmine dye (Matsumoto et al. 2009). Chromoendoscopy identified significantly more lesions than any of the other techniques ($p < 0.05$), particularly flat and depressed polyps. Several studies have also evaluated the role of chromoendoscopy in patients with Hereditary non – polyposis colorectal cancer. The largest published study of 109 patients compared white light colonoscopy with narrow band imaging and chromoendoscopy (Huneburg et al. 2009). Significantly more adenomas and hyperplastic polyps were identified in the chromoendoscopy group. Two smaller studies directly comparing white light colonoscopy with chromoendoscopy reported similar findings, with higher adenoma detection rates, particularly of flat adenomas, in the chromoendoscopy group (Hurlstone et al. 2005; Lecomte et al. 2005). However a study of 292 individuals comparing standard colonoscopy with chromoendoscopy in patients with a personal history of adenomas or family history of colorectal cancer showed similar adenoma detection rates in both groups ($p = 0.18$). Although significantly more diminutive adenomas were detected in the right colon with chromoendoscopy ($p = 0.04$) (Lapalus et al. 2006).

1.6.2 Digital Chromoendoscopy

Endoscope manufacturers have developed push-button technologies, in an attempt to mimic the role of dye based chromoendoscopy. Narrow band imaging (NBI) is termed a pre-processing technology, as it alters the appearance of the index endoscopic image obtained. FICE and I-scan are named post-processing technologies, as the index images obtained by the colonoscope are modified at a later stage using software within the endoscope processor.

1.6.2.1 Narrow Band Imaging (NBI)

Folkman (1971) demonstrated that the growth of tumours was dependant upon angiogenesis and later suggested that this was an important step in carcinogenesis. The notion for the development of a technology that emphasized the vascular change of lesions was later conceived following the observation that capillary patterns were useful in the diagnosis and assessment of upper gastrointestinal malignancy (Gono et al. 2004). Research to develop an endoscopic technology to highlight these patterns was commenced and termed 'narrow band imaging' (NBI). NBI was made commercially available by Olympus Medical systems, Japan in 2005, following the first publication reporting its clinical use a year earlier (Gono et al. 2004).

To understand the principals of NBI it is initially necessary to outline the basic function of the colonoscope. Conventional colonoscopy utilises white light derived from an external xenon light source. White light comprises a spectrum of wavelengths between 400 – 700nm, each corresponding to a different colour. The light is transmitted through a fiberoptic bundle to a light guide lens in the distal tip of the colonoscope, from where it is projected on to the colonic mucosa. Light reflected off the mucosa passes through an objective lens in the colonoscope tip, behind which lies the photosensitive surface of a charged coupled device (CCD). The CCD converts light signals into electronic charges that are changed to an image visible on the video monitor.

Colour images are formed using either RGB (red, green, blue) sequential imaging or colour chip video imaging, each available in different endoscopy systems. RGB imaging uses a rotating filter comprising red, green and blue colour segments that is placed between the xenon light source and fiberoptic bundle. Due to the speed of rotation of the filter, a flickering white light is perceived by the naked eye at the

endoscope tip. During colonoscopy, the mucosal surface is sequentially visualised by light passed through each of these three colours, which is then reflected off the mucosa onto the black and white CCD. Images obtained using each colour are temporarily stored and then reformatted in the video processor to ultimately produce a colour picture. The colour chip CCD has a colour mosaic filter attached in front of the black and white CCD photosensitive surface. Its function is similar to the RGB imaging system.

Haemoglobin, a major component of blood, was targeted in the development of NBI to show the transporting vasculature. Spectroscopy of haemoglobin identifies a maximum absorption peak at a wavelength of 415nm (blue light) and a secondary peak at 540nm (green light). An NBI filter was developed to reduce the wavelength spectrum of white light to these two specific peaks.

NBI is rapidly activated and deactivated using a 'push button' on the control body of the colonoscope. An NBI filter is placed between the xenon light source and fibreoptic bundle, to narrow the bandwidths of light to 415 and 540nm. In the RGB imaging system, this is present in addition to the RGB rotating filter. The narrower 415nm wavelength penetrates the colonic wall more superficially, providing information about the mucosal microvessels where they are identified by their brown colour (Figures 10 and 11). The wider 540nm wavelength penetrates deeper, down to the submucosa (Sano et al. 2006; Song et al. 2008).

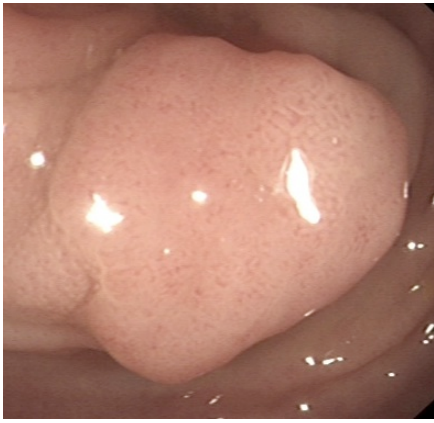


Figure 10 Polyp - white light view

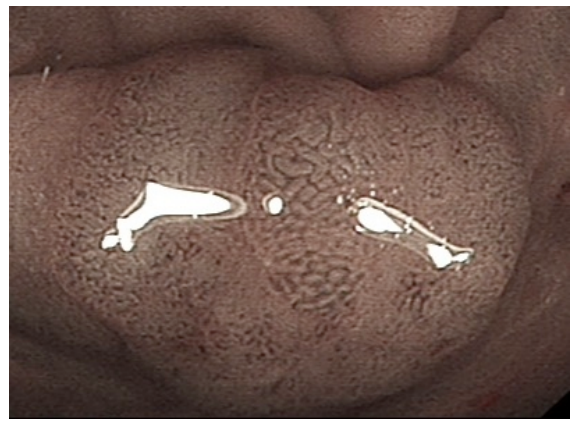


Figure 11 Same polyp with NBI – type II capillary pattern (adenoma)

NBI requires no extra preparation in addition to a normal colonoscopy. However its use may be limited by similar factors to chromoendoscopy, such as poor bowel preparation. NBI is also termed ‘virtual chromoendoscopy’, but has several advantages over the use of dye spraying. It has no additional equipment costs after its initial purchase and is rapidly activated during the procedure by the endoscopist. Concerns have been raised over the potential for methylene blue dye to cause colonocyte DNA damage and subsequent carcinoma risk. However these risks do not appear to be associated with use of indigo carmine dye and are obviated by the use of NBI (East et al. 2007a).

The potential impact of NBI in polyp detection was initially studied in high risk groups. East et al. (2008a) reported adenoma detection rates with NBI compared to standard white light colonoscopy in the proximal colon of 62 patients undergoing HNPCC surveillance. They reported an increase in adenoma detection from 25 with white light to 46 with NBI ($p < 0.001$), particularly of flat adenomas. However this study did not contain a chromoendoscopy arm. This was addressed in a larger study of 109 HNPCC patients, where chromoendoscopy with indigo carmine dye was compared with white light colonoscopy and NBI (Huneburg et al. 2009). Significantly more adenomatous polyps were identified using chromoendoscopy than NBI (22 versus 9, $p = 0.04$),

particularly flat adenomas. NBI has been compared with both chromoendoscopy and AFI for the detection of diminutive neoplasia in a prospective study of 13 patients with FAP (Matsumoto et al. 2009). Chromoendoscopy was superior to NBI in detecting diminutive polyps throughout the colon (43.3 versus 20.1 lesions, $p = 0.003$). A study of 22 patients with Hyperplastic Polyposis Syndrome demonstrated significantly lower polyp miss rates with NBI compared to high definition white light colonoscopy (10% versus 36%, $p < 0.001$) (Boparai et al. 2011). No studies to date have assessed the use of NBI in the moderate colorectal cancer risk group.

1.6.2.2 Fujinon Intelligent ChromoEndoscopy (FICE)

FICE, also termed Computed Virtual Chromoendoscopy (CVC), is available through Fujinon, Japan. As opposed to NBI, no optical filter is required and a standard endoscopic image is initially obtained. This image is modified using a spectral estimation matrix processing circuit in the endoscopy processor, which increases the relative intensity of blue light and decreases the intensity of red and green light according to ten standard settings. Four studies have evaluated the use of FICE in polyp detection to date. Pohl et al. (2009) compared the use of FICE to white light colonoscopy with targeted chromoendoscopy in patients attending for screening or diagnostic colonoscopy. They reported no statistically significant difference in the percentage of patients with ≥ 1 adenoma detected between these two groups ($p = 0.44$). Three further studies comparing FICE with white light colonoscopy have also reported no significant increase in adenoma detection rates (Aminalal et al. 2010; Cha et al. 2010; Chung et al. 2010). However no studies have currently assessed the use of this technology in moderate or high risk patient groups.

1.6.2.3 I-Scan

I-scan is a new post-processing light-filter technology developed by Pentax Medical, Japan. Different images are produced based upon vessel characterisation (v – mode) that highlights the microvasculature, pattern characterisation (p – mode) to categorise the crypt architecture or surface architecture (SE – mode) (Atkinson and Chak 2010). A recent study compared high-definition white light colonoscopy with two different high-definition I-Scan settings in 389 average risk patients undergoing screening colonoscopy (Hong et al. 2012). There was no significant difference in the adenoma detection rates between these groups. A similar prospective study of 210 patients reported higher adenoma detection rates with high-definition I-Scan compared to standard white light colonoscopy (Hoffman et al. 2010a). A smaller study of 69 patients undergoing colonoscopy was performed by the same authors, comparing the use of I-scan with methylene blue chromoendoscopy and high definition (HD) white light, for the detection of diminutive lesions within the distal 30cm of colon (Hoffman et al. 2010b). Lesion detection rates were highest with chromoendoscopy (9.1 lesions) and I-scan (4.7 lesions) and lowest for HD white light endoscopy (2.5 lesions) ($p < 0.001$). Whilst chromoendoscopy identified the highest number of lesions, there was no significant difference in the detection rate of adenomas using I-scan and chromoendoscopy. The application of this technology requires further assessment in clinical trials, including an assessment of its utility in different risk groups.

1.6.2.4 Autofluorescence Imaging (AFI)

Ultraviolet and shorter wavelengths of light when directed at tissue cause excitation of endogenous fluorophores such as collagen and elastin. This excitation results in longer wavelengths of light being emitted, a process termed autofluorescence. Chromophores including haemoglobin simply absorb these shorter wavelengths. The concentration of

fluorophores varies between different layers of the colon, but is predominantly located in the submucosa. Changes in structure of the mucosal layer with neoplastic change alters the amount of emitted light detected.

AFI colonoscopes contain two CCD's, one for standard white light and the other for autofluorescence. Similar to narrow band imaging, AFI is activated through a push button on the control body of the colonoscope. A rotating filter is placed in front of the xenon light source, which divides the light into 390 – 470nm excitation and 540 – 560nm green light (Tajiri 2007). The AFI CCD contains a barrier filter to allow collection of 500 – 630nm reflected light. Image signals from the CCD are formatted in the image processor and displayed in pseudo - colour on the video monitor. Neoplastic lesions have a magenta appearance compared with non – neoplastic lesions which are green.

Matsuda et al. (2008) performed a randomised, back to back pilot study of 167 patients to assess polyp detection with AFI versus white light in the right colon (proximal to the splenic flexure). The overall miss rate for polyps with AFI was significantly less than with white light (30% versus 49%; $p = 0.01$), with fewer neoplastic lesions also missed with AFI ($p = 0.02$). Two studies comparing trimodal imaging (high-resolution colonoscopy, AFI and NBI) with standard colonoscopy have demonstrated no increase in adenoma detection rate or adenoma miss rate with AFI (van den Broek et al. 2009b; Kuiper et al. 2011). A further study of 107 patients reported higher polyp detection with AFI compared with white light, however lack of statistical data prevents additional assessment of validity (McCallum et al. 2008).

AFI has undergone limited appraisal in high risk individuals for colorectal cancer. A study of 13 patients with FAP was performed comparing several imaging techniques including conventional white light, NBI, AFI and panchromoendoscopy (Matsumoto et al. 2009). Chromoendoscopy identified significantly more diminutive lesions than any other modality ($p < 0.05$). More lesions were detected using AFI than white light in the rectum ($p < 0.05$), but no other segment of the colon. No other benefits were conferred with AFI in this cohort of individuals.

1.6.3 High Definition Imaging

High definition (HD) colonoscopes incorporate HD charge coupled devices, in addition to high resolution monitors. The few studies that have compared HD and standard definition colonoscopy have produced mixed results.

A prospective randomised study of 630 patients reported no significant increase in the proportion of patients with adenomas with HD versus standard colonoscopy, but did demonstrate significantly more adenomas per participant (Rastogi et al. 2011). A further prospective study of 390 patients, reported a significantly higher overall polyp detection with HD, but no increase in adenoma detection (Tribonias et al. 2010). A larger retrospective study of 2430 patients showed both increased adenoma and overall polyp detection rates with HD (Buchner et al. 2010).

Four studies have reported no significant increase in adenoma or overall polyp detection rates with HD colonoscopy (East et al. 2008b; Pellise et al. 2008; Burke et al. 2010; Erim et al. 2011). Published data has consistently shown that HD does not increase the detection of advanced adenomas. A meta-analysis combining these studies has shown a

slight increase in overall polyp and adenoma detection with HD colonoscopy compared with standard video endoscopy (Subramanian et al. 2011).

1.7 Factors Affecting The Quality And Yield of Colonoscopy

1.7.1 Bowel Cleansing

Several different types of bowel preparation are commercially available for gastrointestinal investigations including polyethylene glycol (PEG), sodium picosulphate and magnesium citrate. PEG solution is safest in patients prone to fluid or electrolyte imbalance such as those with heart failure or renal impairment (Connor et al. 2012). A recent national audit of 20,085 colonoscopy procedures reported inadequate bowel preparation in 11.8% of cases, with poor bowel preparation cited as the reason for an incomplete procedure in 22.2% of cases (Gavin et al. 2013).

The effectiveness of bowel preparation is affected by the timing of its consumption in relation to the procedure. Polyethylene glycol or sodium phosphate bowel preparations consumed on the same day as colonoscopy result in superior colonic cleansing compared with preparation taken the day prior to the procedure, assessed using non – validated scoring systems, which correlates with increased lesion detection, particularly of flat polyps (Chiu et al. 2006; Parra-Blanco et al. 2006; Chiu et al. 2011). Split dose bowel preparation regimes (i.e. taken both the evening before and the morning of the procedure) have also demonstrated increased adenoma detection compared to bowel preparation taken the night before the procedure (Gurudu et al. 2012).

A retrospective analysis of 93,004 colonoscopies identified from the United States CORI database, reported adequate preparation to be associated with increased detection of polyps $\leq 9\text{mm}$ (OR – 1.23) compared with polyps $> 9\text{mm}$ or suspected cancers (OR – 1.05) using a non - validated scoring system (Harewood et al. 2003). Throughout the

literature, inadequate bowel preparation has been reported to correlate with reduced polyp detection rates (Radaelli et al. 2008; Goncalves et al. 2011; Adler et al. 2013).

A multi - centre prospective observational study of 5832 patients reported no significant affect of bowel preparation upon the diagnosis of colorectal cancer, however the authors did not report the size of malignant lesions (Froehlich et al. 2005). A smaller study reported inadequate bowel preparation to be the reason for missed colorectal cancers in 1.4% of cases (Leaper et al. 2004). The miss rates for advanced adenomas with suboptimal colonic cleansing have been reported between 18 – 27% (Lebwohl et al. 2011; Chokshi et al. 2012).

1.7.2 Antispasmodic Agents

The two main groups of drugs employed as systemic antispasmodic agents in the United Kingdom are anticholinergic agents such as Hyoscine N-butylbromide (Buscopan) and glucagon, which inhibit intestinal motility in humans (Whalen 1974; Lazzaroni and Bianchi Porro 2003).

Whilst the routine use of Buscopan is widely taught and advocated during the withdrawal phase of colonoscopy, there is only limited evidence available regarding its impact upon lesion detection rates. Caution is advised with this drug group in patients with ischaemic heart disease and prostatic symptoms, due to the increased potential for side effects. Concern is also frequently raised in patients with glaucoma, however it is undiagnosed cases that are of greatest risk of complications (Dyde et al. 2008). It is more beneficial to advise patients to seek medical attention with the occurrence of specific ocular symptoms.

A prospective, randomised, double-blinded study of 116 patients compared the use of Buscopan versus placebo upon polyp detection rates (Lee et al. 2010). More polyps per patient were detected in the Buscopan (1.21 ± 2.23) versus the placebo group (0.41 ± 0.91), however this was not statistically significant ($p = 0.06$). A larger, similarly designed study of 674 patients demonstrated no improvement in polyp detection, adenoma detection rates or advanced lesion detection rates with the use of Buscopan compared to placebo (p -values > 0.25) (de Brouwer et al. 2012).

Two separate double - blinded randomised trials including a total of 170 patients, studied the effect of 1mg glucagon versus placebo given prior to colonoscopy and at caecal intubation (Cutler et al. 1995). No difference in colonoscopy insertion or withdrawal times, or polyp yield was identified between the two groups.

1.7.3 Position Change And Luminal Distension

Adequate mucosal visualisation is paramount to maximise the potential for adenoma detection on withdrawal of the colonoscope from the caecum. A study of 1524 patients examined the influence of position change upon lesion detection (Hasuda et al. 2005). Examination from the caecum to the proximal transverse colon was undertaken in a left lateral position. Patients were then moved supine to examine to the distal transverse colon, in a right lateral position to the sigmoid – descending junction and finally back to a left lateral position for completion of the examination. Additional neoplastic lesions were identified in approximately 30% of patients using this technique. East et al. (2007b; 2011) performed similar studies, reporting improved luminal distension in patients undergoing position change as highlighted in the study above and increased polyp and adenoma detection rates. Luminal distension was one factor found to be associated with increased adenoma detection when comparing two experienced

colonoscopists with different adenoma miss rates ($p < 0.001$) (Rex 2000). A back – to – back colonoscopy study also compared a left lateral or supine patient position to a prone position, with no change in adenoma detection rates identified (Rex et al. 1997).

1.7.4 Withdrawal Technique And Rectal Retroflexion

The detection of lesions can be optimised by an adequate withdrawal technique. One study compared two experienced colonoscopists with reported adenoma detection rates of 17 and 48%, who were scored by four expert colonoscopists according to four quality criteria (Rex 2000). The colonoscopist with the lowest miss rates scored significantly higher when assessing the adequacy of fluid removal, degree of luminal distension, time spent viewing the mucosa and examination of the folds, flexures, rectal and ileocaecal valves ($p < 0.001$).

The process of retroflexion involves bending of the distal tip of the colonoscope to look back on itself, allowing direct visualisation of the anorectal area. Rectal retroflexion is currently reported as a colonoscopy quality indicator within the NHS Bowel Cancer Screening Programme (Lee et al. 2012). Five studies totalling 4449 patients, demonstrates an additional adenoma detection of 0.24% in retroflexion compared with forward viewing, whilst the detection of other benign pathologies is higher (Cutler and Pop 1999; Hanson et al. 2001; Varadarajulu and Ramsey 2001; Saad and Rex 2008; Reddy et al. 2011). However this small increase in yield has to be balanced against the risk of rectal perforation, reported at 0.01% in a study of 39,054 colonoscopy procedures (Quallick and Brown 2009).

1.7.5 Colonoscopy Withdrawal Times

A landmark prospective study of 2053 colonoscopy procedures showed higher neoplasia detection rates in endoscopists with a withdrawal time of ≥ 6 minutes (28.3%) compared with those < 6 minutes (11.8%) ($P < 0.001$) (Barclay et al. 2006). Advanced neoplastic lesions (lesions ≥ 10 mm, a villous component, high grade dysplasia or cancer) were also more likely to be identified with a longer withdrawal time (6.4% versus 2.6%, $p = 0.005$). A larger retrospective analysis of 10,955 colonoscopies recorded a median endoscopist withdrawal time of 6.3 minutes (Range: 4.2 – 11.9 minutes) (Simmons et al. 2006). Multivariate analysis identified a longer withdrawal time to be a significant predictor of higher polyp detection rates, with an odds ratio of 11.8 ($p = 0.005$). The majority of polyps were ≤ 5 mm, of which 56% were adenomas. A statistically significant correlation was seen between the mean endoscopist withdrawal time and for polyps ≤ 5 mm ($p < 0.0001$), but not for larger polyps. The authors advised a minimum withdrawal time of 7 minutes. Similar findings were reported in a smaller study, which reported no increase in polyp detection rate for lesions ≥ 5 mm in size irrespective of a withdrawal time ≥ 6 minutes (Moritz et al. 2012). Several additional studies have demonstrated a correlation between withdrawal times of up to 8 minutes and increased adenoma detection rates (Sanchez et al. 2004; Barclay et al. 2008; Benson et al. 2010; Overholt et al. 2010; Lee et al. 2012). However a single study of 23,910 procedures has reported no increase in polyp detection for a withdrawal time of ≥ 7 minutes irrespective of polyp size (Sawhney et al. 2008). The authors concluded that improved polyp detection might relate to other components of an endoscopist's technique that enhance mucosal visualisation.

Additional studies are required to clearly determine the effect of withdrawal time versus other factors upon polyp detection rates. However based upon available evidence, a withdrawal time from the caecum of greater than 6 minutes for diagnostic colonoscopy, has been established as a quality indicator in bowel cancer screening programmes internationally (Rex et al. 2006; Chilton and Rutter 2011).

1.8 Risks of Colonoscopy

Diagnostic and therapeutic colonoscopy confers a risk of complication, predominantly of perforation and haemorrhage. Increased procedural risks are associated with increasing patient age, co - morbidity, diverticulosis and a lower rate of procedures performed by the colonoscopist (Gatto et al. 2003; Rabeneck et al. 2008; Arora et al. 2009; Singh et al. 2009). For diagnostic procedures, perforation rates of up to 0.13% and haemorrhage rates of 0.001% are reported (Sieg et al. 2001; Misra et al. 2004). A large retrospective study of 277,434 procedures reported the perforation risk of diagnostic colonoscopy at 0.07% (Arora et al. 2009). The risks associated with therapeutic colonoscopy are higher than for diagnostic procedures, but vary with the nature of intervention undertaken. A perforation rate of 1.1% and major haemorrhage rates of 1.6% have been reported for snare polypectomy (Heldwein et al. 2005). Heldwein et al. (2005) reported polyp location in the right colon as a risk factor for major complications (odds ratio 2.40, 95% CI 1.34 – 4.28). Lower perforation rates of 0.58% are reported for endoscopic mucosal resection (EMR) procedures (Figure 12), in which fluid is injected into the submucosal space to prevent deeper thermal injury (Taku et al. 2007). A recent national UK audit of 20,085 diagnostic and therapeutic colonoscopy procedures reported an overall perforation rate of 0.04% and bleeding rate of 0.26% (Gavin et al. 2013).

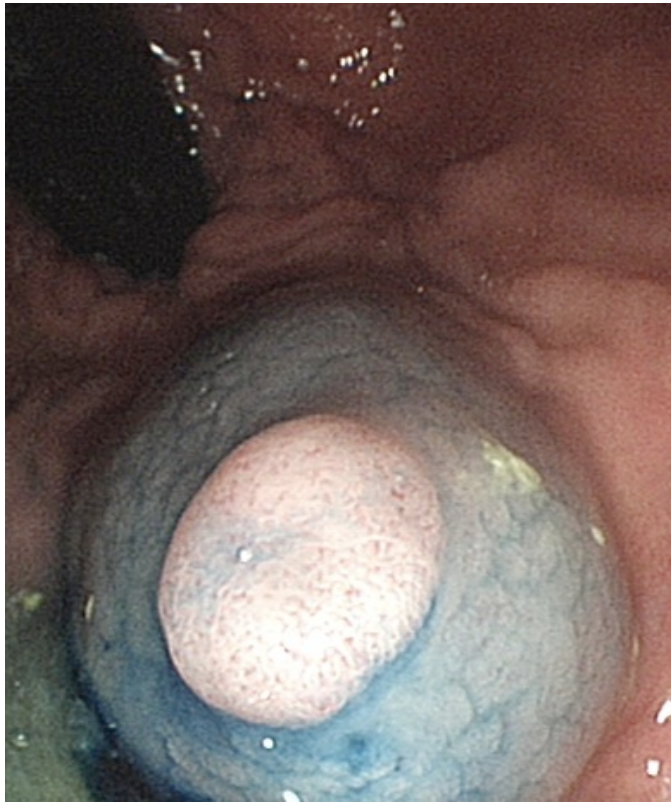


Figure 12 Rectal adenoma raised with 'EMR solution' prior to polypectomy (NB: presence of blue indigo carmine dye in the injection solution to define the submucosal plane)

2. Accuracy and concordance between in situ and post-fixation measurements of colorectal polyp size and their potential impact upon surveillance intervals.

2.1 Background

The malignant potential of a polyp is influenced by its histological type (i.e. villousness), size and grade of dysplasia (Muto et al. 1975; O'Brien et al. 1990). These factors are used to determine polyp surveillance intervals according to national and international guidelines (Cairns et al. 2010; Lieberman et al. 2012). Polyp size may be measured at various time points: in situ by the endoscopist using visual estimation and reference points such as open or closed biopsy forceps, pre-fixation in formalin following polyp retrieval or post-fixation in formalin by the histopathologist. Recommendations in surveillance guidelines related to polyp size are founded upon two landmark studies, one of which recorded the in situ measurement using biopsy forceps and the other histological polyp size (O'Brien et al. 1990; Atkin et al. 1992). However this variance in the method of data collection has meant that the polyp size measurement used to determine surveillance categories within both national and international adenoma surveillance guidelines has not been confirmed (Cairns et al. 2010; Lieberman et al. 2012).

Current national (UK) adenoma surveillance guidelines divide patients into three different categories: (i) Low risk: 1 to 2 subcentimetre adenomas, (ii) Intermediate risk: 3 to 4 small adenomas or at least one ≥ 1 cm, and (iii) High risk: ≥ 5 small adenomas or ≥ 3 at least one ≥ 1 cm (Cairns et al. 2010). Patients falling into the low risk category within the Bowel Cancer Screening Programme (BCSP) return to two yearly screening with Guaiac faecal occult blood (FOB) testing (NHS BCSP 2009). These

recommendations differ from international guidelines that also incorporate the histological polyp type and grade of dysplasia (Lieberman et al. 2012).

2.2 Study aims

1. To assess the projected clinical impact of differences in polyp size measurements obtained in situ, pre-fixation and post-fixation upon current surveillance intervals.
2. To determine the most accurate measurement device to record post-fixation polyp size, comparing the ruler, callipers and graduated magnifying lens.

2.3 Ascertainment of cases and methodology

Consent for the study was provided by Bowel Screening Wales. All four Cardiff and Vale University Health Board screening colonoscopists (Dr Sunil Dolwani, Dr Barney Hawthorne, Dr John Green, Mr Jared Torkington) agreed to participate in the study. The size of consecutive polyps meeting the study inclusion criteria were visually estimated in situ by the colonoscopist, and then measured pre-fixation by either the clinical research fellow (CRF) or Specialist Screening Practitioner (SSP) and by a consultant histopathologist post-fixation. Training sessions were provided to all participants to standardise measurement techniques. The study inclusion criteria included polyps: (a) resected 'en bloc' (i.e. in a single fragment), (b) diameter \leq 35mm, and (c) resected by cold biopsy, snare polypectomy or endoscopic mucosal resection (EMR). Exclusion criteria included polyps: (a) resected piecemeal (i.e. in more than one fragment), (b) $>$ 35mm in size, (c) removed by hot biopsy, and (d) those fragmenting into more than one piece during retrieval.

The colonoscopist visually estimated the in situ polyp size, using open or closed biopsy forceps (Radial Jaw 3. Boston Scientific, Natick, USA. Closed diameter 2.2mm and open diameter 8mm) or snare (Cook Medical Europe Ltd, Limerick, Ireland. Sheath diameter 2.5mm and open snare diameter 25mm) as a reference point. An endoscopy nurse recorded measurements on a standard proforma sheet, blinded to the CRF or SSP. Polyps were then resected by cold biopsy, standard snare or endoscopic mucosal resection (EMR) depending upon their size and morphology. All EMR procedures were performed using a standard solution containing 43mls of gelofusine, 5mls of 0.8% indigo carmine dye and 2mls of 1:10,000 adrenaline. The polyp retrieval method was chosen according to their size, to minimise trauma or distortion and included biopsy forceps, a polyp suction trap (Bracco Diagnostics Inc, Princeton, USA) or Roth net (US Endoscopy, Mentor, USA). Following retrieval all polyps were placed on a glass slide to allow them to resume their 'natural shape'. The maximal polyp diameter or length was measured by the CRF or SSP using a standard metal ruler. The pre-fixation measurement was defined as 'gold standard', in line with previous studies (Gopalswamy et al. 1997; Schoen et al. 1997). Only the macroscopic adenomatous component of any sample was incorporated in the measurement. For polyps with a pedunculated morphology, measurement excluded the stalk. Each individual specimen was placed in 10% formalin for transport to the histopathology department.

A consultant gastrointestinal histopathologist, blinded to all previous measurements, recorded the maximal polyp diameter or length using three different devices post-fixation (ruler, calliper and graduated magnifying lens). These devices were used to measure each lesion in a randomised order to minimise potential bias. Polyps were placed on a glass slide or work bench for measurement. Polyp size measurements throughout this study were recorded to the nearest millimetre.

2.3.1 Statistical analysis

Statistical analysis for this study was undertaken using Stata software (StataCorp LP, Texas, USA). A sample size calculation indicated that a sample of 43 polyps would have a 90% power to detect a 1mm difference in mean in situ and pre-fixation measurements, using a one-sample t-test with a significance level of 0.05 assuming a standard of the differences of 2mm (Margulies et al. 1994; Moug et al. 2010). Bland-Altman plots were used to assess agreement between polyp measurements taken at the different time points (in situ, pre-fixation and post-fixation) (Bland and Altman 1986). One sample t-tests were performed to determine whether the mean difference in measurements was statistically significant from zero, and 95% limits of agreement calculated.

Measurements were categorised according to BCSP and BSG guidelines ($< 10\text{mm}$ and $\geq 10\text{mm}$) and sensitivities and specificities calculated for in situ and post-fixation measurements, taking pre-fixation measurements to be the study gold standard result (NHS BCSP 2009; Cairns et al. 2010). The post-fixation measurement was taken as most accurate when compared to in situ measurements, to study the effect of polyp measurement upon surveillance intervals.

Post-fixation measurement devices were compared using the Kruskal-Wallis test as the data was skewed. Bland-Altman plots were also produced to illustrate the level of agreement between the measurement devices. A p-value of < 0.05 was deemed as statistically significant throughout.

2.4 Results

107 polyps were studied from 65 patients. The CRF measured 88 (82.2%) of the polyps pre-fixation, with the remaining 19 (17.8%) measured by a SSP. Patient demographics and polyp characteristics are shown in Table 3.

Patient demographics			
Age, mean \pm SD		64 \pm 6.7 years	
Gender, n (%)		Male 45 (69.2) Female 20 (30.8)	
Polyp characteristics			
Polyp location, n (%)	Caecum	14 (13.1)	
	Ascending colon	11 (10.3)	
	Hepatic flexure	2 (1.9)	
	Transverse colon	7 (6.5)	
	Splenic flexure	4 (3.7)	
	Descending colon	9 (8.4)	
	Sigmoid colon	42 (39.3)	
	Rectosigmoid colon	4 (3.7)	
Paris classification, n (%)	Rectum	14 (13.1)	
	Is (sessile)	22 (20.6)	
	Isp (subpedunculated)	34 (31.8)	
	Ip (pedunculated)	27 (25.2)	
	IIa (flat elevated)	23 (21.5)	
	IIaIIc (flat elevated with depressed centre)	1 (0.9)	
	Polyp resection method, n (%)	EMR	59 (55.1)
		Standard snare	41 (38.3)
Cold biopsy		6 (5.6)	
Cold snare		1 (0.9)	
Polyp retrieval method, n (%)	Polyp trap	35 (32.7)	
	Roth net	66 (61.7)	
	Biopsy forceps	6 (5.6)	

SD, standard deviation; n, number; EMR, endoscopic mucosal resection

Table 3 Patient demographics and polyp characteristics

The median in situ polyp size was 7mm (Interquartile (IQ) range: 4mm, 12mm), pre-fixation ruler size 8mm (IQ range: 4mm, 12mm) and post-fixation ruler size 8mm (IQ range: 5mm, 12mm).

Comparison of polyp measurements in situ, pre and post-formalin fixation

The differences between polyp readings being studied are presented on the y-axis and are plotted against the average of the two readings on the x-axis, in the Bland-Altman plots in Figures 13 a-c. The red lines demonstrate the mean and limits of agreement.

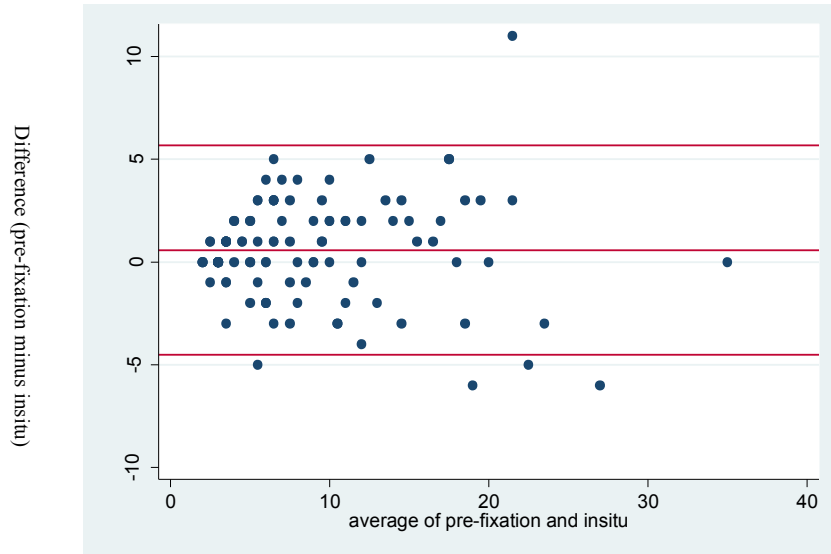


Figure 13a Bland-Altman plot of the difference between the pre-fixation ruler and in situ measurements

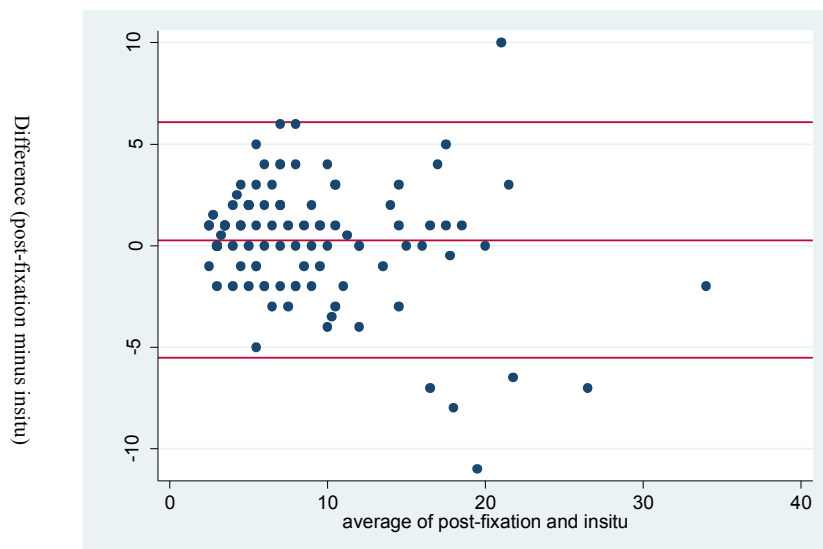


Figure 13b Bland-Altman plot of the difference between the post-fixation ruler and in situ measurements

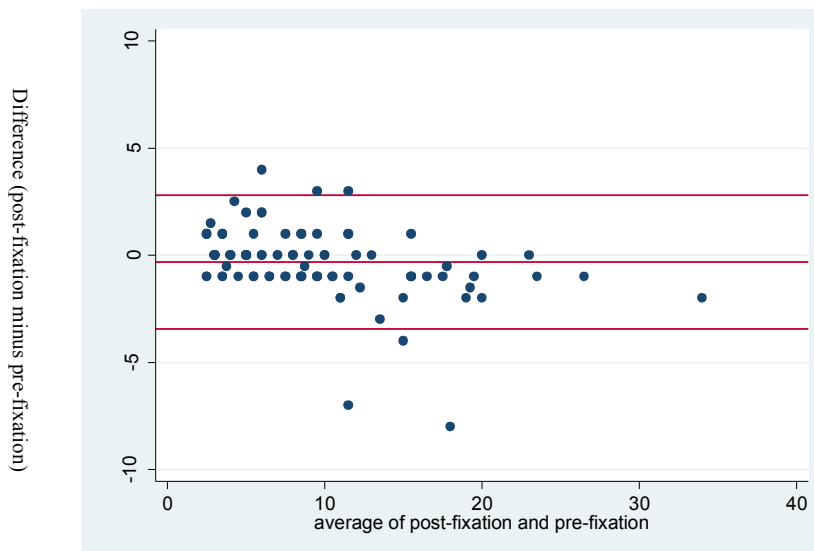


Figure 13c Bland-Altman plot of the difference between the post-fixation and pre-fixation ruler measurements

The mean (SD) of the difference between the pre-fixation ruler and in situ measurement was 0.58mm (2.54mm), with a 95% limit of agreement of -4.51mm to 5.67mm. This demonstrates that for a randomly selected new polyp, the differences between the in situ and pre-fixation measurements would be expected to lie within these limits 95% of the time. A one sample t-test of the differences against zero showed a significant difference between the two measurement methods ($p = 0.02$), indicating that on average the pre-fixation ruler measurements are higher.

The mean (SD) of the difference between the post-fixation minus the pre-fixation ruler measurement was -0.32mm (1.56mm), with a 95% limit of agreement of -3.44mm to 2.80mm. A one sample t-test of the differences against zero showed a significant difference between the two measurement methods ($p=0.04$), indicating that on average ruler measurements were lower after fixation.

The mean (SD) of the difference between the post-fixation ruler and in situ measurement was 0.26mm (2.96mm), with a 95% limit of agreement of -5.51mm to 6.09mm. A one sample t-test of the difference against zero, demonstrated no evidence of a difference between the two measurements ($p = 0.36$).

Using an unpaired t-test, no significant difference was observed between the in situ and pre-fixation measurements using the Polyp trap or Roth net for polyp retrieval ($p = 0.56$).

Effect of polyp measurements on surveillance intervals

Current national BSG and Bowel Cancer Screening Programme adenoma surveillance guidelines use a polyp size threshold of ≥ 10 mm to distinguish between low and intermediate risk groups (NHS BCSP 2009; Cairns et al. 2010). Tables 4 a-c show the effect of different polyp measurements on this categorisation.

		Pre-fixation polyp size		
		<10mm	≥ 10 mm	Total
In situ polyp size	< 10mm	65	8	73
	≥ 10 mm	2	32	34
	Total	67	40	107

(a)

		Post-fixation polyp size		
		<10mm	≥ 10 mm	Total
Pre-fixation polyp size	< 10mm	65	2	67
	≥ 10 mm	4	36	40
	Total	69	38	107

(b)

		Post-fixation polyp size		
		<10mm	≥ 10mm	Total
In situ polyp size	< 10mm	64	9	73
	≥ 10mm	5	29	34
Total		69	38	107

(c)

Table 4 The impact of polyp measurements taken at different time points upon surveillance intervals: (a) comparing in situ and pre-fixation ruler measurements, (b) comparing pre-fixation and post-fixation ruler measurements and (c) comparing in situ and post-fixation ruler measurements

Using the pre-fixation ruler measurements as gold standard, ten (9.3%) patients would be classified differently by in situ measurements according to these guidelines (Table 4a). Eight (7.5%) patients might not receive surveillance procedures soon enough and two (1.9%) may be investigated too early. This gives a sensitivity of 80% (95% CI: 64% to 91%) and specificity of 97% (95% CI: 90% to 100%). Using the pre-fixation ruler measurements as gold standard, six (5.6%) patients would be classified differently by post-fixation measurements according to current guidelines (Table 4b). Four (3.7%) might not undergo surveillance early enough and two (1.9%) patients may be investigated too early. This gives a sensitivity of 90% (95% CI: 76% to 97%) and specificity of 97% (95% CI: 90% to 100%). If the post-fixation measurements were used as standard, fourteen (13.1%) patients would be classified differently by in situ measurements according to existing guidelines (Table 4c). Nine (8.4%) patients might receive delayed surveillance procedures and five (4.7%) patients may be investigated too early. This gives a sensitivity of 76% (95% CI: 63% to 90%) and specificity of 93% (95% CI: 87% to 99%).

Post-fixation measurement devices

When comparing polyp size using the three different post-fixation measurement devices, the median and interquartile range was similar across all devices (Figure 14).

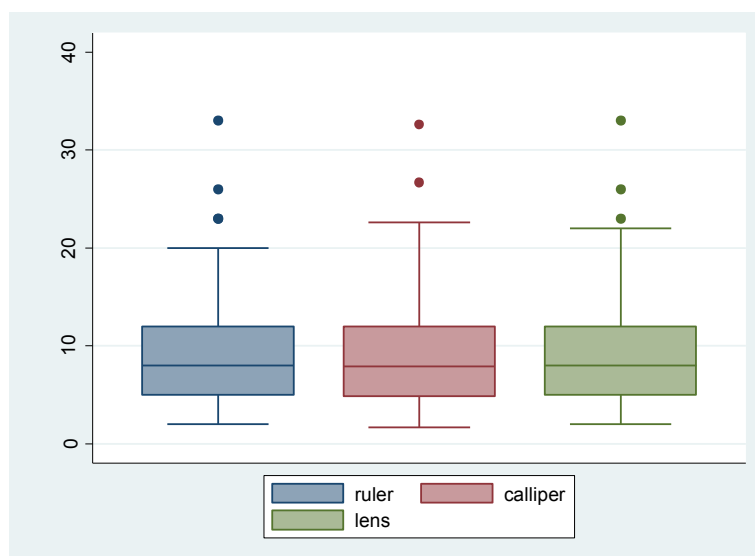


Figure 14 Box and whisker plot of measurement devices used to record polyp size by the pathologist post-fixation.

The median diameter was 8.0mm using the metal ruler, 8.0mm using a graduated magnifying lens, and 7.9mm using the callipers. The mean (SD) of the difference between the ruler and calliper device was -0.11mm (0.67mm), with a 95% limit of agreement of -1.45mm to 1.23mm. The mean (SD) of the difference between the ruler and the graduated magnifying lens was 0.07mm, (0.55mm) with a 95% limit of agreement of -1.04mm to 1.17mm. The mean (SD) difference between the calliper and magnifying lens was 0.17mm (0.66mm), with a 95% limit of agreement of -1.15mm to 1.50mm.

Using Bland-Altman plots, the agreement between measurement devices is shown in Figures 15 a-c. The Kruskal-Wallis test demonstrated that no significant difference in polyp size was observed between these devices ($p = 0.89$).

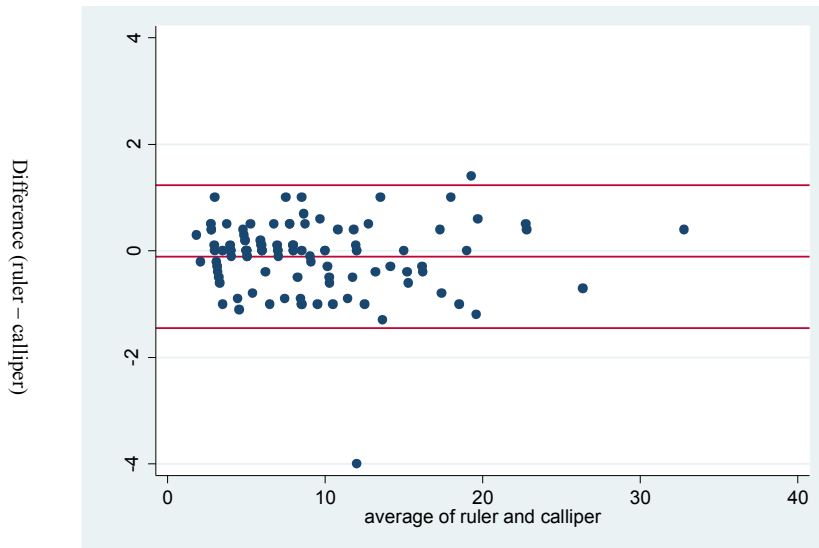


Figure 15a Bland-Altman plot showing the agreement in post-fixation polyp size between the ruler and calliper

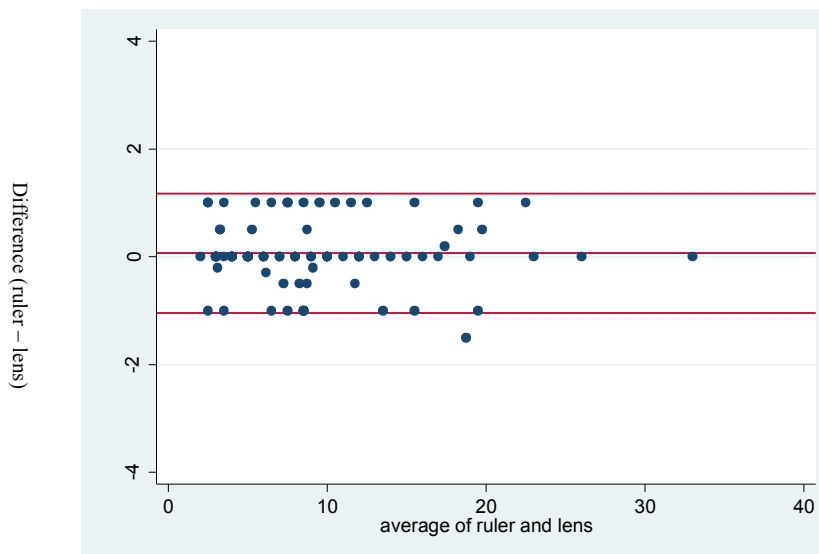


Figure 15b Bland-Altman plot showing the agreement in post-fixation polyp size between the ruler and graduated magnifying lens

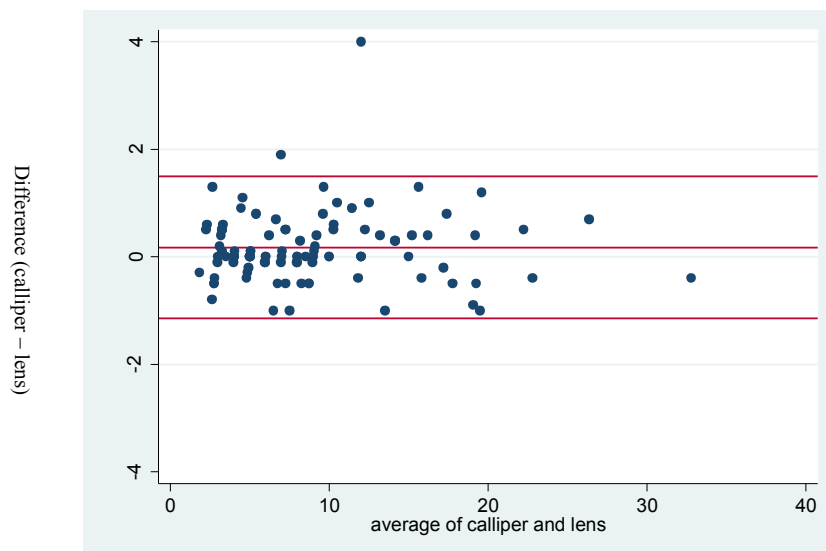


Figure 15c Bland-Altman plot showing the agreement in post-fixation polyp size between the calliper and magnifying lens

2.5 Discussion

The results of this study show that both the colonoscopist and histopathologist significantly underestimate polyp size compared to the study gold standard (pre-fixation measurement), with this difference being greatest for the colonoscopist (Figures 13a-c). In vitro studies utilising artificial polyp phantoms have consistently reported the colonoscopist to underestimate polyp size (Fennerty et al. 1993; Margulies et al. 1994; Rubio 2007). Previous human studies have shown mixed results, confounded by inclusion of a small number of cases and a large number of participating colonoscopists. Moug et al. (2010) studied the variation in size measurements of 35 polyps reported by seven different colonoscopists and also reported underestimation of polyp size. Two studies have reported overestimation of in situ polyp size but either exclusively or predominantly (72%) included polyps with a pedunculated morphology (Morales et al. 1996; Schoen et al. 1997). However these lesions have the potential for greater variation in measurement due to their increased mobility and stalked component. This study included polyps of different morphologies and representative of those identified within

the BCSP (Table 3). Formalin fixation has previously been reported not to influence polyp size as so was not included in this study (Schoen et al. 1997; Moug et al. 2010).

This study reports a narrower 95% limit of agreement for post-fixation than in situ measurements compared with pre-fixation measurements (study gold standard). This supports the use of the histopathologists (post-fixation) measurement to determine surveillance intervals, as recommended in the European colorectal cancer screening pathology quality assurance guidance (Quirke et al. 2011). Compared with the study gold standard, post-fixation measurements are also associated with a lower variance in surveillance group stratification than with in situ measurements (5.6% vs. 9.3%). Both polyp number and size are the two factors that determine an individual's surveillance interval within current national and BCSP guidance (NHS BCSP 2009; Cairns et al. 2010). Whilst polyp number is not considered in this study, based upon polyp size alone, the majority of patients would potentially move into a lower risk category with less frequent surveillance. This is of greater significance to patients outside of the BCSP who might have an additional delay of 2 years in their surveillance interval, compared with participants within this programme who would resume 2 yearly FOB testing (NHS BCSP 2009). These findings equally impact patients undergoing surveillance procedures internationally, with polyp size remaining an important determinant of surveillance intervals (Lieberman et al. 2012).

A polyp size of 1cm has been established as an arbitrary threshold for surveillance stratification based upon historical data, with studies demonstrating increased malignant potential for polyps equal or greater than this size (Muto et al. 1975, O'Brien et al. 1990; Atkin et al. 1992). However this malignant risk is part of a continuum and it should be remembered that it is unlikely to be significantly different for a polyp of

9.9mm compared to one that is 10.1mm. Of further clinical importance is awareness of endoscopists and reporting histopathologists of the phenomenon known as ‘terminal digit preferencing’. This is where an individual may round the final digit up or down, most commonly to a value of zero. Studies of colorectal adenomas and adenocarcinoma have demonstrated a preference for the digits zero and five, having the potential to influence an individual’s surveillance risk group (Hayes 2008; Hayes 2009).

Only en bloc resections were included in this study to allow a direct comparison of measurements. Whilst not directly compared to the pre-fixation measurement, the median in situ polyp size was similar to the post-fixation size ($p = 0.36$). This suggests that for piecemeal resections, that in the absence of a histopathologist’s measurement the in situ size could be used as an adequate alternative to determine surveillance intervals. Piecemeal resection is most commonly required for larger polyps, but may also be required in cases of challenging polyp access (eg: lesion wrapped around a fold) or due to submucosal fibrosis secondary to previous resection attempts. In the absence of commercially available graduated endoscopic measurement devices, an open snare may be used to estimate the size of larger lesions, but usually relies upon an educated estimation by the colonoscopist. Any increase in polyp size above 1cm does not influence an individual’s surveillance interval, but does determine the malignant potential of the lesions in addition to conferring an increased risk of advanced adenomas at follow up (Muto et al. 1975; Martinez et al. 2009). Measurement by the histopathologist in this scenario is often unreliable due to the numerous fragments provided. Endoscopic submucosal dissection (ESD) is a newer technique that allows en bloc resection of such lesions as well as adequate histological assessment, but is limited by the level of expertise in this procedure throughout the UK (NICE IPG 335. 2010).

This study is the first to compare post-fixation measurement devices that may be used in routine clinical practice. No significant difference in polyp size measurement was observed between the three different devices, using the Krukshall-Wallis test ($p = 0.89$) (Figures 14 and 15). In the absence of any difference we recommend use of the ruler as gold standard due to its widespread availability and ease of use. Concern has been raised that callipers may compress a polyp, influencing its size (Rubio 2007). However this most likely reflects the technique used. One potential source of study bias was measurement of each polyp using these devices by the same histopathologist. However the pathologist used these devices in a random order for each polyp measured to minimise this.

We established the pre-fixation measurement as the gold standard, similar to previous authors (Gopalswamy et al. 1997; Schoen et al. 1997). There is currently no commercially available graduated endoscopic measurement device and so in situ measurements were recorded using visual estimation utilising other endoscopic devices such as biopsy forceps or snare as a guide. Each colonoscopist was provided with a teaching session to minimise variation. In addition, any endoscopic retrieval method has the unavoidable potential to traumatise and distort the shape of a polyp, affecting the pre and post-fixation measurements. This was minimised by ensuring the technique used was appropriate for both the polyp size and morphology. Biopsy forceps might be thought to result in more significant damage to a lesion, however only six polyps were retrieved using this method. Exclusion of these measurements did not influence the statistical results. The majority of polyps (61.7%) were retrieved using the Roth net, with lesions held loosely to minimise any compression or distortion. Prior to their pre-fixation measurement on a glass slide, the polyps were allowed to resume their 'natural' shape.

This study provides evidence supporting the use of post-fixation polyp size measurements as advised in the European pathology colorectal cancer screening recommendations (Quirke et al. 2011). However there is a clear need for future studies to determine the effect of different polyp size measurements upon specific outcome measures such as the subsequent risk of neoplasia. The endoscopist currently routinely books future surveillance colonoscopy at the time of the procedure. These results demonstrate that the surveillance interval should be determined with information from the histopathology report.

3. Interobserver agreement in the reporting of colorectal polyp pathology among histopathologists in Wales.

3.1 Background

The reporting of histological specimens inevitably results in a varying degree of interobserver agreement amongst pathologists, irrespective of their experience. This may differ with the type of tissue analysed and reporting categorisation used. However the clinical significance of this variation depends upon the parameter studied in relation to published guidelines. Colorectal pathology reporting considers several factors including polyp type, grade of dysplasia and the margin excision status. Previous studies comparing the interobserver agreement in the reporting of colorectal histology have generally included a small number of participants and focused upon specific areas of histopathology reporting (Costantini et al. 2003; Denis et al. 2009).

The bowel cancer screening programme (BCSP) was initially introduced in England in 2006 and later commenced in Wales in October 2008, with the ultimate aim of identifying and resecting benign colorectal pathology, thereby reducing the incidence of colorectal cancer in the future. In 2007, the BCSP pathology group published national guidelines titled 'Reporting lesions in the NHS bowel cancer screening programme' (NHS BCSP 2007). This document outlines the preparation and principal diagnostic features of lesions encountered within the programme, including adenocarcinoma. European recommendations for the quality assurance of pathology in colorectal cancer screening and diagnosis were later published in 2011 (Quirke et al. 2011). A variety of colorectal pathology is identified through such screening programmes. Lesions posing diagnostic uncertainty are initially discussed with a second local pathologist or regional specialist gastrointestinal (GI) pathologist. Complex cases in which doubt remains can

be referred to the UK reference panel for a consensus opinion from a group of nationally and internationally renowned GI experts.

Within Wales, histopathologists become involved in the bowel screening programme following agreement with their local health board and usually have an interest in gastrointestinal pathology. Unlike colonoscopy, there is no formal initial assessment and accreditation of screening histopathologists. The existing quality assurance consists of a combination of on-line external quality assessments (EQA) and annual study days. The EQA includes up to fourteen slides and reporting sheets distributed to approximately 150 histopathologists nationally. Suboptimal performance is initially addressed through feedback to the individual, with assistance offered. However sustained underperformance is addressed through a national (UK) quality assurance panel.

3.2 Study Aims

1. To determine the interobserver agreement in the reporting of colorectal polyps between Bowel Cancer Screening pathologists in Wales and a gold standard (Professor of gastrointestinal pathology), and its potential clinical impact.
2. To study specific examples of non-invasive lesions known to cause diagnostic uncertainty.

3.3 Ascertainment of cases and methodology

Twelve non-invasive colorectal lesions were selected from pathology and gastroenterology databases, by a consultant bowel cancer screening histopathologist. These cases included a combination of serrated polyps and conventional adenomas with varying grades of dysplasia and completeness of excision (margin excision status)

commonly seen within the screening programme. In addition, five cases (2, 3, 4, 6 and 11) with histology known to pose diagnostic uncertainty in clinical practice were selected (epithelial misplacement/ pseudoinvasion, a sessile serrated lesion (polyp) without conventional dysplasia squamous metaplasia and focal high grade dysplasia) (Table 5). Between two to five histological sections of the polyp were included on each slide to allow adequate assessment of these factors. The ‘gold standard’ for this study consisted of answers provided by a Professor of gastrointestinal pathology, who was also co-author of the reporting guidelines and member of the national expert histopathology panel.

Case	Histological features (Gold standard for the study)			Endoscopic features		
	Polyp type	Grade of dysplasia	Pathologist excision	Pathologist comments	Resection method	Endoscopist excision
1	VA	High	Incomplete		Snare	Complete
2	TA	Low	Complete	Epithelial misplacement	Snare	ND
3	HP (SSL)	NA	Incomplete		EMR	Complete
4	TVA	Low	Complete	Squamous metaplasia	EMR	ND
5	SA	Low	Uncertain		EMR	Complete
6	TA	High	Complete	Focal high grade dysplasia with epithelial misplacement	Snare	ND
7	VA	Low	Complete		Snare	ND
8	SA	Low	Incomplete		EMR	Complete
9	TVA	High	Complete		Snare	ND
10	TA	Low	Incomplete		EMR	ND
11	TA	High	Uncertain	Focal high grade dysplasia with cytological atypia	Snare	ND
12	HP	NA	Uncertain		Snare	ND

EMR, endoscopic submucosal resection; HP, hyperplastic polyp; NA, not applicable; ND, not documented; SA, serrated adenoma; TA, tubular adenoma; TVA, tubulovillous adenoma; VA, villous adenoma

Table 5 Histological and endoscopic polyp features

Conventional adenomas can either be defined as tubular, tubulovillous or villous. BCSP guidelines differentiate these polyp types based upon the WHO classification, with an estimated volume of villous component less than 20% considered tubular, between 20 – 79% as tubulovillous and 80% or more as a villous adenoma (Hamilton and Aaltonen 2000; NHS BCSP 2007). The grade of dysplasia within an adenoma is

defined as either low or high grade. High grade dysplasia is predominantly diagnosed on architectural features, supplemented by cytology (NHS BCSP 2007).

An outline of the study was first presented at an annual BCS histopathology study day in 2008. Consent for the study was granted by Bowel Screening Wales. A list of all histopathologists participating in bowel cancer screening at the time of the study and their contact details was provided by the pathology quality assurance lead for Wales, in addition to a list of all study day attendees. Detailed information was sent to all participants prior to commencing the study in February 2009. A slide delivery date and one week reporting period was agreed with each histopathologist, consistent with BCS histopathology group recommendations. The only study exclusion criterion was failure to report the slides within this time period. Electronic and paper copies of the reporting sheets (Appendix 1) were issued by the clinical research fellow (CRF) along with a single box set of slides. Each sheet provided tick boxes to record the polyp type, grade of dysplasia and completeness of histological excision. They were advised to record the most severe grade of dysplasia identified on each slide. A free text section was also included for any additional comments. Participants were requested to report their findings independently and without collaboration with colleagues to minimise bias. The publication 'Reporting lesions in the NHS Bowel cancer screening programme' was used as the reporting standard and is available in all histopathology laboratories throughout Wales, in addition to being available via the Internet (NHS BCSP 2007). The contents of this publication were discussed at great length during the study day. Each histopathologist was allocated an anonymised identification number using block randomisation, only known to the participant and CRF. Study data was collated by the CRF. Information regarding the endoscopists' resection technique and completeness of

resection recorded at the time of the procedure were obtained from the endoscopy reporting system (ADAM, Fujinon).

3.3.1 Statistical analysis

Statistical analysis was performed using Stata version 10 software (StataCorp LP, Texas, USA). Interobserver agreement between histopathologists for each of the categories studied was performed using Kappa statistics as presented by Fleiss, which allows for multiple observers and the fact not all observers classified all subjects (Table 6) (Fleiss 1981). Confidence intervals were calculated using bootstrapping, as standard errors cannot be easily obtained for cases where the number of observers per subject is not constant (Efron 1982). This is a distribution independent technique, using data from a sample population, in this case the histopathologists. Repeated samples are taken a large number of times, known as ‘bootstrap samples’. A sample summary is then used to produce confidence intervals. Missing values can cause a statistical problem in bootstrapping. If the number of missing values is relatively small to sample size, this should make little difference. To check this was the case both ‘best-case’ and ‘worse-case’ scenarios were evaluated. In the ‘best-case’ scenario a mode was calculated for the values provided. The mode was then imputed into any missing values. Whilst for the ‘worst-case’ the category furthest away from the mode was calculated. This value was then imputed into any missing values. The bias-corrected percentile method was used to construct confidence intervals using 1000 repetitions, to allow for the possible lack of symmetry in the sampling distribution of kappa.

Kappa value	Level of agreement
0.00	Chance
0.00 – 0.20	Slight
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Substantial
0.81 – 1.00	Almost perfect
1.00	Perfect

Table 6 Kappa statistics (Fleiss 1981; Silcocks 1983)

3.4 Results

Twenty eight out of an eligible twenty nine histopathologists in Wales were included in the study. One histopathologist was excluded due to failure to report the slide set within the allocated one week time period.

There were a total of eight missing values in the data collected. Only 25 out of 28 participants for case 3 recorded the completeness of lesion excision. Two pathologists did not provide a grade of dysplasia for case 6 and one pathologist did not give a dysplasia grade for case 11 (both cases contained focal high grade dysplasia); one pathologist did not provide a polyp type or grade of dysplasia for case 3 (sessile serrated lesion/hyperplastic polyp). The inputting of missing values for these cases made little difference to the confidence intervals and no difference to the interpretation of results. Figure 16 demonstrates the agreement between the histopathologist and gold standard for each of the parameters studied.

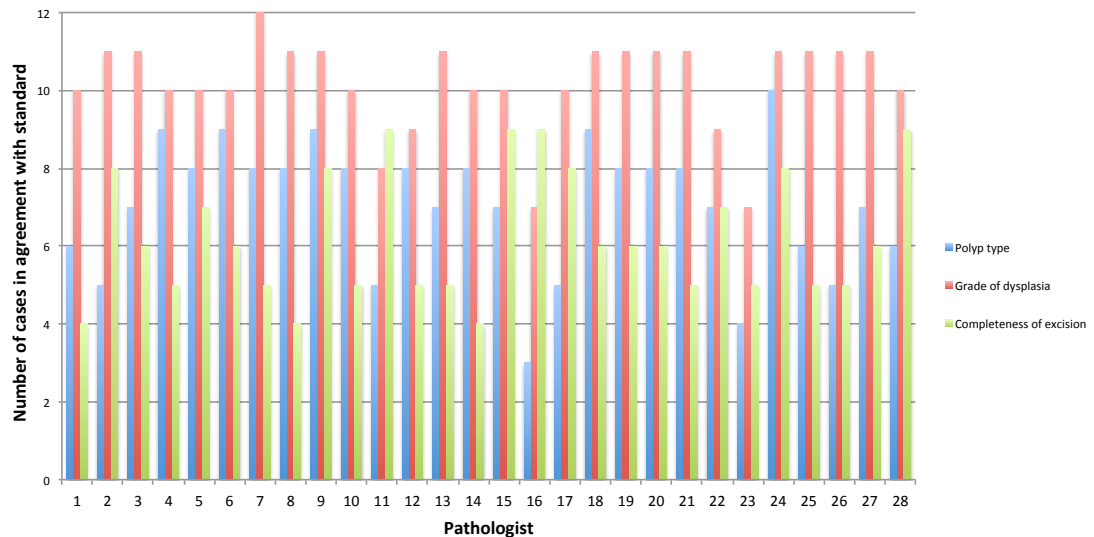


Figure 16 Comparison of the histological factors studied for each participant compared with the gold standard

Polyp type

The overall kappa coefficient for the reporting of polyp type (where the five possible categories were hyperplastic polyp, serrated adenoma, tubular adenoma, tubulovillous adenoma and villous adenoma) was 0.45 (95% CI: 0.34 to 0.59), indicating ‘moderate’ agreement, with the confidence interval spanning over ‘fair’ to ‘moderate’ agreement.

There was 96.1% concordance between participants and the gold standard in distinguishing neoplastic from non-neoplastic lesions (i.e. those with and without dysplasia). Four pathologists classified an adenomatous lesion as non-neoplastic and eight classified one or two non-neoplastic lesions as adenomatous. All of these discrepancies involved the differentiation of hyperplastic polyps from serrated adenomas (Table 7). None of the four serrated lesions in the study set were classified in accordance with the gold standard by all 28 pathologists; eight participants ‘misclassified’ one case and a further eight ‘misclassified’ two or three cases.

Case	Standard	Percentage of pathologists in agreement with the gold standard
3	HP (SSL)	81
5	SA	71
8	SA	64
12	HP	86

HP, hyperplastic polyp; **SA**, serrated adenoma; **SSL**, sessile serrated lesion

Table 7 Differentiation of serrated adenomas from hyperplastic lesions

The remaining eight lesions in the study selected as examples of conventional adenomas, were classified as neoplastic lesions by all participants. Two of these (cases 10 and 11) were classified as serrated adenomas by 3 of the 28 and 1 of the 28 pathologists respectively (Figures 20 & 21). More importantly, two cases (6 and 11) were diagnosed as invasive adenocarcinoma by five pathologists and one pathologist respectively (Figures 18 & 21). Both of these were examples of adenomas with focal high grade dysplasia and case 6 also showed epithelial misplacement (pseudoinvasion) in the head of the polyp (Figure 18). None of the pathologists diagnosed adenocarcinoma in the other case with epithelial misplacement selected for the study (case 2).

Further subclassifying conventional adenomas into tubular, tubulovillous and villous types also showed some discrepancies (Table 8). While villous adenomas (cases 1 and 7) and tubulovillous adenomas (cases 4 and 9) were correctly identified by all 28 pathologists, all four tubular adenomas (cases 2, 6, 10 and 11) were ‘misclassified’ as tubulovillous adenomas by 39%, 65%, 48% and 15% of participants respectively and one tubular adenoma was classified as a villous adenoma by one participant. Only 5 out of 28 pathologists classified all four cases in accordance with the gold standard.

Case	Standard	Percentage of pathologists in agreement with the gold standard
1	VA	100
2	TA	61
4	TVA	100
6	TA	30
7	VA	100
9	TVA	100
10	TA	52
11	TA	85

TA, tubular adenoma; TVA, tubulovillous adenoma; VA, villous adenoma

Table 8 Differentiation of villous (VA/TVA) from non-villous (TA) adenomas

Grade of dysplasia

The kappa coefficient for the reporting of the grade of dysplasia (high, low or no dysplasia) was 0.67 (95% CI: 0.50 to 0.86) indicating ‘substantial’ agreement, with the confidence interval spanning over ‘moderate agreement’ to almost perfect’ agreement. Table 9 demonstrates pathologists’ agreement with the gold standard for the ten adenoma cases used in the study.

Case	Standard	Percentage of pathologists in agreement with the gold standard
1	High	96
2	Low	96
4	Low	43
5	Low	96
6	High	77
7	Low	100
8	Low	86
9	High	100
10	Low	100
11	High	56

Table 9 Reporting of the grades of dysplasia

Despite the overall favourable kappa correlation coefficient for grading of dysplasia, a number of important discrepancies were identified (Table 9). High grade dysplasia, albeit focal, was not reported by 44% of participants in case 11 (Figure 21) and one case

of high grade dysplasia was said by one pathologist to have no dysplasia despite classifying the lesion of a tubular adenoma (this was probably an error of data sheet entry). Conversely, one case selected to show low grade dysplasia (case 4) was diagnosed as high grade by the majority of participants (Figure 17). 15 out of 28 pathologists classified one or two high grade lesions as low grade, and 17 of the 28 classified one or two low-grade lesions as high grade. Two pathologists reported discordant dysplasia grades from the gold standard in four of the ten adenoma cases: one ‘overrated’ the grade of dysplasia for one lesion and ‘underrated’ the grade of dysplasia for three lesions; the other ‘overrated’ two cases and ‘underrated’ two cases.

Completeness of excision

The kappa coefficient for the histological reporting of the degree of excision (complete, incomplete or uncertain) was 0.24 (95% CI: 0.07 to 0.43), indicating ‘fair’ agreement, with the confidence interval spanning over ‘slight agreement’ to ‘moderate’ agreement. Three of the twelve cases (5, 11 and 12) had been selected for the study on the basis that completeness of excision was considered to be uncertain (Table 5); excluding these from the analysis made little difference to the calculated kappa coefficient 0.26 (95% CI: 0.08 to 0.45).

Five lesions were selected on the basis that they appeared completely excised (Table 5). In only one of these cases did all pathologists concur, and a categorical statement of incomplete excision was made by three and five of the 28 pathologists in two of the cases. Complete excision was said to be uncertain by 14 and 13 of the 28 pathologists respectively for these two cases, and by a minority (2 out of 28 and 7 out of 28 respectively) in the other two cases.

Four lesions were considered incompletely excised when selected for the study on the basis of lesional epithelium at a diathermised margin in the section circulated, but no more than 11 of the 28 pathologists were able to confirm this categorically in any one case. Remarkably 5, 7 and 8 pathologists respectively stated that excision was unequivocally complete for three of the cases. Pathologists appeared to show a reluctance to make a decision on completeness of excision in most of these four cases: four pathologists reported uncertain excision in all four cases and a further sixteen were uncommitted in at least two cases.

Training session

Fifteen of the twenty eight participants attended the initial bowel cancer screening training day. Each of the different reporting components was compared for both of these groups (Table 10).

Polyp factor	Attended training session Kappa value (95% CI)	Non-attendance at training session Kappa value (95% CI)
Polyp type	0.44 (0.29 – 0.60)	0.46 (0.35 – 0.57)
Grade of dysplasia	0.59 (0.40 – 0.79)	0.79 (0.63 – 0.94)
Completeness of excision	0.25 (0.07 – 0.44)	0.21 (0.04 – 0.39)

Table 10 Reporting of the colorectal polyp histology according to attendance at the study day.

3.5 Discussion

This study invited all bowel screening histopathologists within Wales to participate and included carefully selected cases, allowing us to focus on potential areas of diagnostic uncertainty in pathology reporting.

There was a high level of agreement between the participants and standard in distinguishing adenomatous from non-adenomatous polyps (96.1%), as previously reported (van Putten et al. 2011). Reporting of the polyp type had a moderate level of agreement ($k = 0.45$). There was over reporting of the villousness of tubular adenomas in between 15 – 70% of cases (Table 8). This is likely to relate to the subjective nature of reporting the villous component according to WHO criteria, where a villous component of $< 20\%$ is defined as tubular (Hamilton and Aaltonen 2000). Previous studies have reported similar findings (Yoon et al. 2002; van Putten et al. 2011; Foss et al. 2012). Whilst this would not alter the surveillance category of patients according to national guidelines, it does influence the malignant potential of a lesion (BCSP 2009; Cairns et al. 2010). These results have more significant implications for international screening programmes, where such factors are important in determining surveillance intervals (Lieberman et al. 2012). One of the principal areas of difficulty arose in participants differentiating hyperplastic from serrated adenomas (Table 7). 16 histopathologists misclassified one or more cases. This reflects the challenges faced with the evolving classification of serrated lesions. Previous interobserver agreement studies specifically assessing serrated lesions have reported overall kappa values at between 0.14 – 0.55 (slight to moderate level of agreement) (Glatz et al. 2007; Farris et al. 2008; Bustamante-Balen et al. 2009; Wong et al. 2009).

One particularly unexpected finding of this study, was the inadequate level of agreement amongst pathologists in assessing the excision margin status of colorectal lesions ($k = 0.24$). This area of histological reporting has been poorly investigated in previous studies and is only discussed in national and European reporting guidelines in the context of invasive lesions (NHS BCSP 2007; Quirke et al. 2011). There was frequent reporting of uncertain excision by participants, with 13 histopathologists

documenting it for a minimum of 50% of cases. 18% of participants reported complete excision in a polyp with advanced histological features (case 1), which was reported as incompletely excised by the standard. A further 18% of participants reported incomplete excision in case 6, which was reported as completely excised by the standard. This has the potential to influence an endoscopist's recommendation regarding the timing of future surveillance, particularly for advanced adenomas such as those with high grade dysplasia. One study weakness was the inability of participants to obtain additional histological levels, however all histopathologists were provided with identical information to allow the level of agreement in reporting to be determined. In clinical practice both a polyp's morphology and the resection technique employed by the endoscopist may influence reporting of the excision margin status, especially where adenomatous tissue may be present up to the diathermy margin, not infrequently occurring with polyp resection techniques such as endoscopic mucosal resection. Excision margin status should ultimately combine pathological and endoscopic results. However excision status was only included on the endoscopy report in a third of cases (Table 5). This could be improved by including it as a mandatory data entry field in endoscopy reporting systems. It is also a topic area that requires further attention in future BCS pathologist training sessions.

Of significant concern was the reporting of invasive adenocarcinoma by six histopathologists in two cases (6 and 11), both of which contained focal high grade dysplasia (Figures 18 and 19). Case 6 (reported as adenocarcinoma by five pathologists) was associated with epithelial misplacement, a phenomenon where adenomatous epithelium passes through the muscularis mucosa into the submucosa, which is recognised to pose diagnostic uncertainty (NHS BCSP 2007). Outside of a study setting, this case may have prompted review by colleagues, a regional specialist or referral to

the expert panel, but equally had the potential to significantly impact patient management, with all five pathologists reporting either incomplete or uncertain excision, compared with a complete margin excision status reported by the gold standard. This could have resulted in unnecessary radiological staging and referral for surgical resection. It would also result in avoidable patient anxiety associated with a diagnosis of malignancy. However, reassuringly no reports of invasive malignancy were reported in the second case of epithelial misplacement that was associated with low grade dysplasia (case 2).

Overall, there was a substantial level of agreement in determining the grade of dysplasia ($k = 0.67$), which is comparable to previous studies (Costantini et al. 2003; van Putten et al. 2011; Foss et al. 2012). Two cases (4 and 11) were highlighted as causing particular difficulty (Table 9). The first contained squamous metaplasia (morules), which led the majority of participants to over report the grade of dysplasia (Figure 17). The second case (case 11) was a tubular adenoma containing a focus of high grade dysplasia (Figure 19). Outside of these two cases, improvement in the levels of agreement in this area of reporting is less likely to be amenable to simple training than with other histological factors, as there was no consistent over or under grading of dysplasia either by individual pathologists or more globally.

The use of tick box reporting sheets in this study gave rise to missing data in a minority of cases and probable error of data entry in one case of an adenoma being reported as having no dysplasia. In clinical practice this is overcome by use of an all Wales on-line histopathology reporting system – ‘CHIRP’ (Cancer Histopathology Information Reporting Project). This is intelligent software that provides a choice of answers appropriate to the response provided. For instance if a lesion is marked as being adenomatous then it will only give the choice of the lesion having low or high grade

dysplasia, not including no dysplasia. A standardised report is then generated for the endoscopist and specialist screening practitioner.

Attendance at the initial study day does not appear to have improved the reporting of histopathological specimens. It may be that the method or content of material taught on the study day was inadequate to enhance understanding in these areas or alternatively participants may have been presented with too much information resulting in their over interpretation and analysis of slides. It is also possible that those histopathologists with less confidence in gastrointestinal histopathology reporting attended the meeting. The results of this study will inform future study day organisers of areas requiring focused training, such as the assessment of excision margin status. Whilst some websites include generic examples of different GI pathology encountered (eg: www.virtualpathology.leeds.ac.uk), this could be developed further to include e-learning modules tackling some of the problem areas highlighted in this study, allowing education of individuals at their own pace. The development of dual reporting of histologically advanced specimens and widespread introduction of regional multi-disciplinary to discuss complex or unusual lesions would also be of benefit. A more radical consideration would be introduction of a formal accreditation process, as exists for screening colonoscopists. However this would inevitably confer significant resource implications for the screening programme.

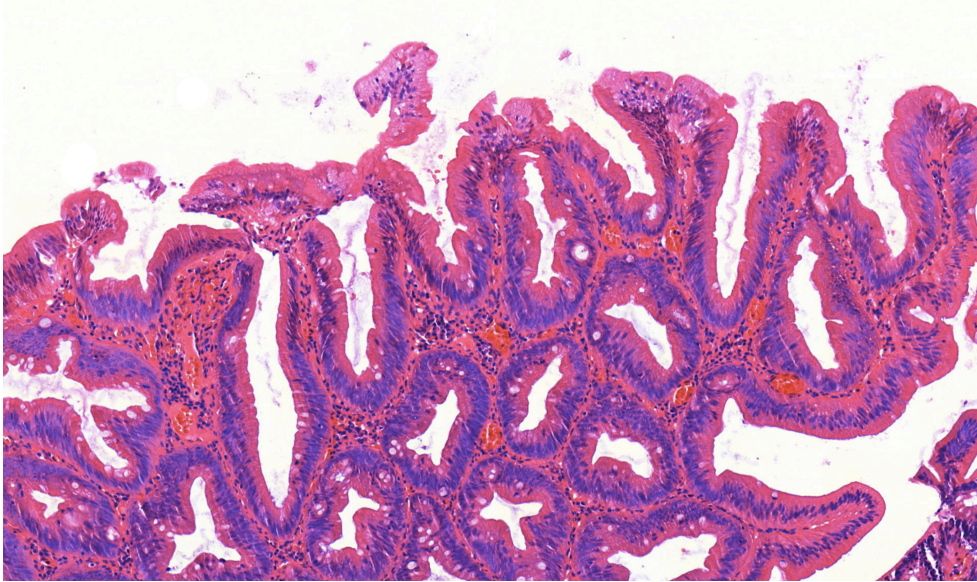
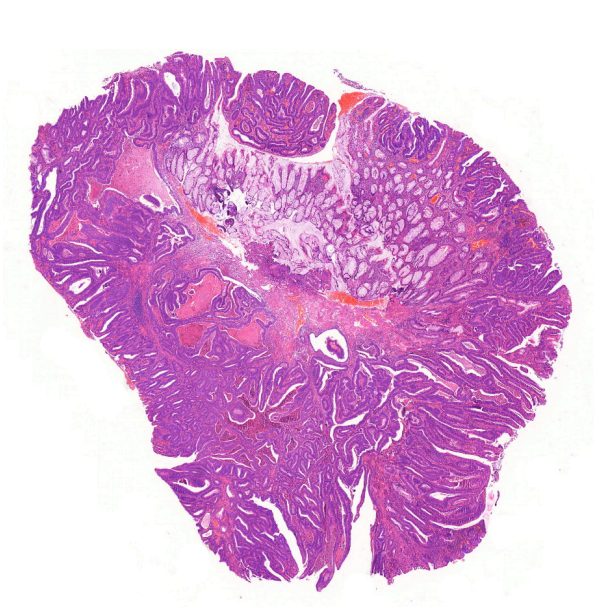
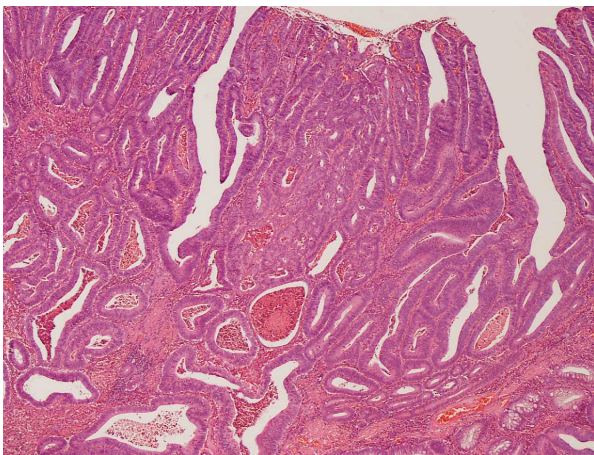


Figure 17 Traditional serrated adenoma with low grade dysplasia (Case 8)



(a) Low power field



(b) High power field

Figure 18 Epithelial misplacement with focal high grade dysplasia (Case 6)

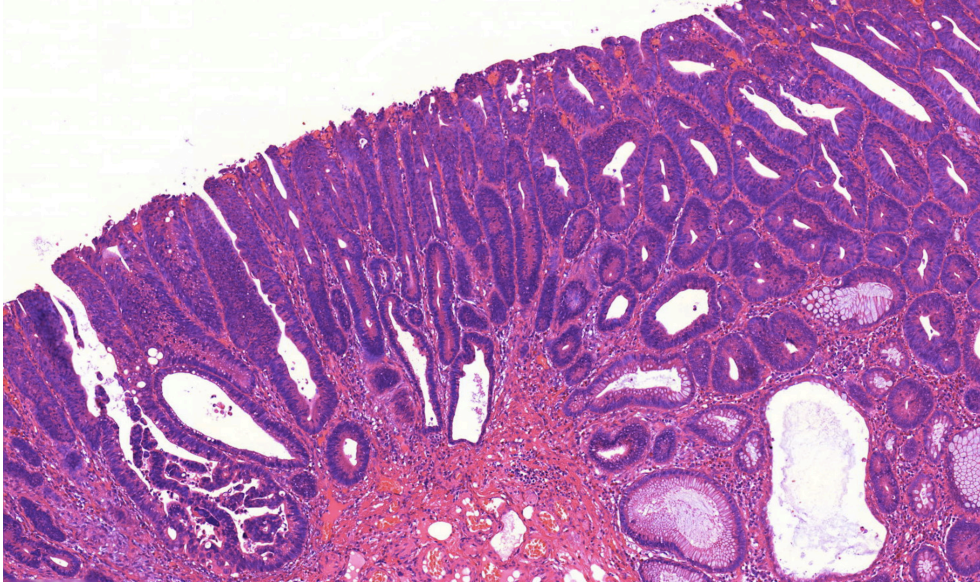


Figure 19 Tubular adenoma with focal high grade dysplasia (Case 11)

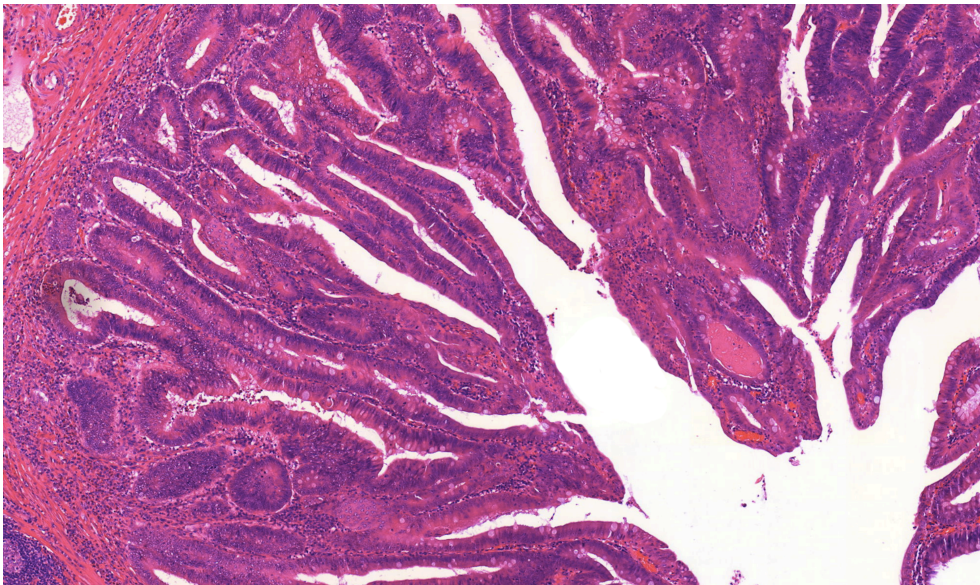


Figure 20 Tubulovillous adenoma with squamous metaplasia (case 4)

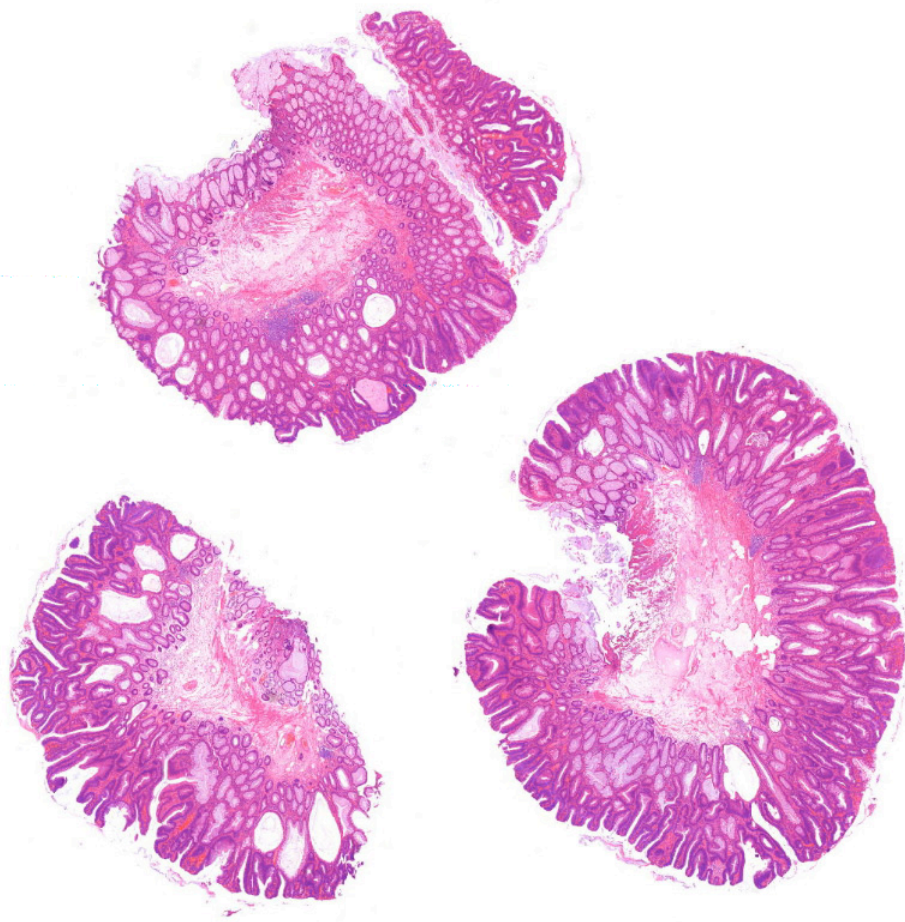


Figure 21 Tubular adenoma with low grade dysplasia (Case 10)

4. Referral pathways through a regional medical genetics service in patients with a moderate family history risk of colorectal cancer.

4.1 Background

The organisation of medical genetic services internationally varies with different health care systems (Hodgson et al. 1999). However access to centres with multidisciplinary team and psychological input appears consistent throughout Europe (Hopwood et al. 2003). There is also regional variation in the set up of services throughout the UK, with consultations held in designated cancer genetics clinics, general genetic clinics and other hospital clinics (Wonderling et al. 2001).

The Cancer Genetics Service for Wales (CGSW) includes three regional referral centres based in Cardiff (South East Wales), Swansea (South West and Mid Wales) and Rhyl (North Wales) and was commissioned in 1998 following publication of the Harper report, which recommended reorganisation of genetics services across England and Wales (Working Group for the Chief Medical Officer 1998). Consultation with primary care during development of this service, acknowledged that general practitioners were not able to support high quality genetic assessment or counselling (Elwyn et al. 2000; Elwyn et al. 2002). Each centre provides an array of services including the risk stratification and counselling of individuals with a family history of different malignancies such as colorectal, breast and ovarian cancer. Colorectal referrals account for the second largest group of patients referred to cancer genetics services throughout the UK, reflecting the high incidence of colorectal cancer (Wonderling et al. 2001; Globocan 2008).

Referrals to the medical genetics department are accepted from primary care and hospital speciality teams including gastroenterology, oncology and colorectal surgery, for those fulfilling guidelines published by the all Wales multidisciplinary consensus group (Table 2). The complexity of referral pathways may vary depending upon a patient's first point of contact. The process for patient assessment and notification of risk stratification has evolved in response to a rising demand for the service (Phelps et al. 2004). Patients are currently sent a postal questionnaire to ascertain demographic information, personal risk factors for malignancy and their relevant family history. Following attempted confirmation of the history provided through medical records, death certificates and cancer services, patients are stratified as average, moderate or high risk of colorectal cancer following multi-disciplinary discussions involving the three genetic counsellors and consultant clinical geneticists. Average risk patients are discharged from the service with a detailed personalised letter explaining their risk stratification and providing general lifestyle advice. Moderate risk patients are usually provided with a similar letter (Appendix 2), but containing additional advice regarding appropriate surveillance intervals and the option of telephone discussion. The risk stratification letters provide individuals with a permanent record of their stratification. In a published survey of our regional centre, 80% of patients reported being quite or very satisfied with this approach (Phelps et al. 2004). Patients stratified as high risk or those in who further information may be required (includes some of the moderate risk group), are invited to attend a genetic counselling clinic. Genetic testing may also be discussed with individuals during these appointments where applicable. A copy of the letter is sent to the referring physician and general practitioner (if not the referring physician), including any recommendations for future colonoscopic surveillance. Similar referral and assessment strategies have been adopted by other centres throughout the UK (Metcalf et al. 2009). Whilst the referral pathway to cancer genetic

services has been refined, the patient journey following risk stratification has not previously been described.

4.2 Study aims

1. To determine the referral pathways which currently exist through a regional (South East Wales) genetics service for patients with a high-moderate family history risk of colorectal cancer.
2. To review the surveillance recommendations made by the genetics department for individuals at a high-moderate family history risk of colorectal cancer.
3. To determine the subsequent colonoscopic surveillance of patients who were referred from primary care and non-gastrointestinal speciality teams.

4.3 Ascertainment of Cases and Methodology

Patients referred to the South East Wales Cancer Genetics Service (Cardiff) between the 1st January 2000 and 1st May 2010 that were assessed and coded as being at high-moderate risk of colorectal cancer were identified from a search of the genetics section of the CaNISC (Cancer Network Information System Cymru) database. Patients were defined as high-moderate risk after review of information supplied in the questionnaire by the genetics counsellors and discussion with clinical geneticists. Only three low-moderate risk individuals were identified and therefore excluded from data analysis. Demographic data and information regarding referral pathways through primary and secondary care was obtained through a combination of CaNISC and patient genetics department and general medical records. Information regarding colonoscopic procedures was acquired through the Cardiff and Vale University Health Board Patient Management System (PMS) and endoscopy database (ADAM, Fujinon). An individual's perceived lifetime risk of cancer is recorded as a component of the genetics questionnaire. Any patient fulfilling the moderate risk referral criteria but who had not

received formal assessment by the genetics service and patients stratified as low or high risk of colorectal cancer were excluded from data analysis.

4.4 Results

243 patients were stratified as high-moderate risk by the cancer genetics department during the study period. A median of 15.5 referrals (range: 5 – 58) was received annually between 2000 – 2009 (Figure 22).

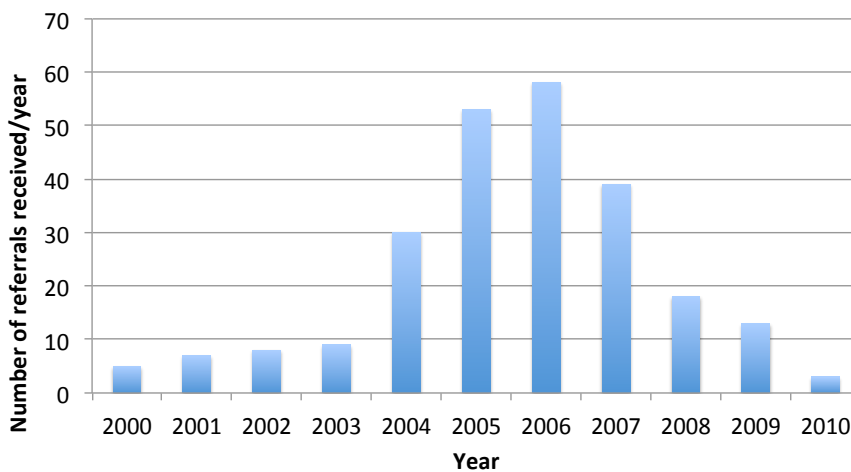


Figure 22 Annual number of referrals received for patients stratified as high-moderate risk

Patient demographic details are recorded in table 11. The mean patient age at referral was 48.4 years old (95% CI: 46.9 – 49.9), ranging from 16 – 78 years old. The majority (60.9%) of patients were aged 40 – 59 years old at the time of referral. There was a female preponderance in a ratio of 2.4 to 1.0.

Sex	Patient number (%)
Male	71 (29.2)
Female	172 (70.8)
Age at referral (years)	
< 20	1 (0.4)
20 – 29	13 (5.3)
30 – 39	42 (17.3)
40 – 49	73 (30.0)
50 – 59	75 (30.9)
60 – 69	33 (13.6)
70 – 79	6 (2.5)

Table 11 Patient demographics

230 (94.7%) patients returned their genetics assessment postal questionnaire. Of the remaining thirteen patients: six were reviewed directly in clinic and seven had information gathered from previous risk assessments undertaken for a relative. In addition to collecting patient demographic and family history data, this questionnaire invites individuals to estimate their perceived lifetime risk of developing cancer between 0 – 100% by marking a diagram. This is performed prior to any intervention or information provided by the medical genetics team. Its value is to allow the team to accurately identify individuals with significant anxieties, so that these can be addressed accordingly. 156 patients completed this question with a mean score of 56.2% (95% CI: 52.9 – 59.6), ranging from 10 – 100% (Figure 23).

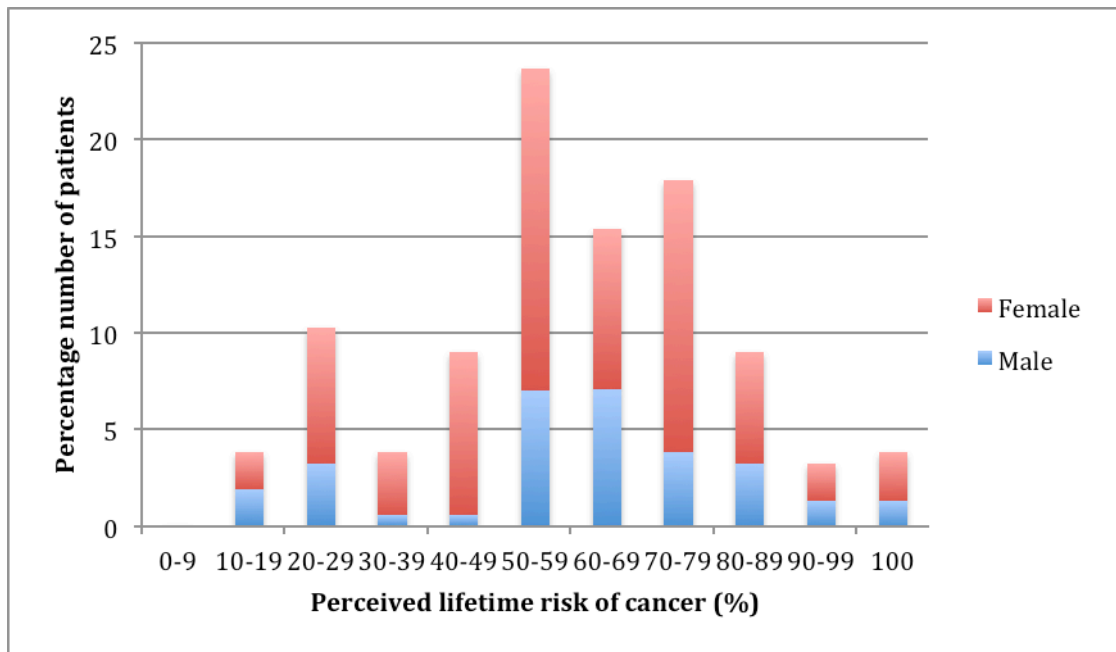


Figure 23 Lifetime risk of developing cancer perceived by patients

186 patients (76.5%) received their stratification and surveillance recommendations through a personalised risk assessment letter. The remaining 57 patients (23.5%) were reviewed in a genetic counselling clinic in addition to receiving written correspondence regarding their risk stratification. The recommended colorectal surveillance intervals are recorded in table 12. The majority (93.8%) of patients were advised to undergo colonoscopy at a 5 yearly surveillance interval. Of the patients categorised as ‘other’, five were advised to undergo a one off colonoscopy due to their age at referral and one patient was advised to undergo procedures at the age of 50 and 60.

Recommended surveillance interval	n (%)
3 yearly	3 (1.2)
5 yearly (no age recommendation)	165 (67.9)
5 yearly (from a defined age)	63 (25.9)
3 – 5 yearly	6 (2.5)
Other	6 (2.5)

Table 12 Surveillance intervals for the high-moderate risk group following genetics review

63.4% of referrals to the cancer genetics service were received from primary care (Table 13). A further 30.4% of referrals were received from secondary care, from specialities including gastroenterology, colorectal surgery and oncology. Re-referral to the genetics department was made for eight patients (3.3%) due to lack of awareness of a previous referral. The average length of time from receipt of the questionnaire by the genetics department to the risk assessment letter or clinic review was 169 days (95% CI: 149 – 189). This includes the time required for verification of information provided in the questionnaires against hospital records, cancer registries and death certificates.

Referral routes	n (%)
Single written referral made during the patient pathway	
Genetics (patient self presentation) → Gastro	2 (0.8)
Genetics (patient self presentation) → GP (<i>a</i>)	4 (1.6)
Two written referrals made during the patient pathway	
GP → Genetics → GP (<i>b</i>)	105 (43.2)
GP → Genetics → Gastro	20 (8.2)
GP → Genetics → Surg	5 (2.1)
Oncology → Genetics → Oncology (<i>c</i>)	2 (0.8)
Three written referrals made during the patient pathway	
GP → Gastro → Genetics → Gastro	27 (11.1)
GP → Surg → Genetics → Surg	36 (14.8)
GP → Surg → Genetics → Gastro	9 (3.7)
GP → Genetics → GP → Gastro	18 (7.4)
Four written referrals made during the patient pathway	
GP → Gastro → GP → Genetics → GP (<i>d</i>)	3 (1.2)
GP → Surg → GP → Genetics → GP (<i>e</i>)	6 (2.5)
GP → Genetics → GP → Surg → Gastro	6 (2.5)

Gastro, Gastroenterology; **GP**, General Practitioner; **Surg**, Surgical

Table 13 Referral pathways through the cancer genetics service. Each arrow indicates a written referral made from one specialist or department to another (eg: GP → Genetics denotes a written referral made from the patients general practitioner to the medical genetics department). The letters in italics refer to specialities that do not have direct access to surveillance colonoscopy.

All patients (n = 9) from pathways (a), (c) and (d) were referred for colonoscopic surveillance. Five out of six patients following pathway (e) were referred for colonoscopy. Of the 105 patients following pathway (b): 70 have undergone

colonoscopic surveillance, 28 patients have been advised to commence surveillance at a future date, 3 patients did not attend scheduled colonoscopy appointments and 4 patients have not been referred for endoscopy (two patients were greater than 75 years old).

4.5 Discussion

The majority (63.4%) of referrals received by the cancer genetics service for the high-moderate risk group are generated from primary care. 2.4% referrals occurred through patient self-presentation, although this is generally discouraged to avoid saturation of the cancer genetics service from the 'worried well'. There has been a fall in the number of referrals received for the high-moderate risk patient group from fifty-eight in 2006 to thirteen in 2009. Although the reasons for this are not clearly apparent, it is feasible that knowledge of the introduction of the Bowel Screening Programme in Wales in 2008 may have influenced referral numbers in later years. Within this screening programme, Faecal Occult Blood (FOB) testing is currently offered to individuals aged between 60 – 75 years old on a two yearly basis. This age group accounts for around a sixth of patients referred to the regional centre in this study. A proportion of individuals may decide to participate in this screening programme rather than seek referral for genetics risk stratification. In addition, symptomatic patients with a family history of colorectal cancer referred to secondary care may also be reassured by normal invasive investigations such as colonoscopy and not seek or be referred for formal genetics assessment. It should also be noted that this study only includes patients that have had contact with the medical genetics service. There will be an additional cohort of patients that have undergone colonoscopy for an undefined family history risk, in addition to individuals that may have a family history of colorectal cancer that has not been considered by the reviewing physician.

The national awareness and early diagnosis initiative (NAEDI) was announced in 2007 and forms a collaboration between the Department of Health, National Cancer Action Team and Cancer Research UK with the aim of improving patient awareness of a number of malignancies including colorectal, prostate and ovarian cancer. Following an initial pilot, the national bowel cancer awareness campaign was rolled out in 2012 through media sources including television, radio, the press and through face-to-face events in the community. Whilst unlikely to have affected the results of this study, it may influence future patient pathways through primary and secondary care, with an increase in symptomatic patients presenting for investigation. This provides opportunity for assessment of an individual's family history. However there is also a risk that this may be overlooked in lieu of a patient's symptoms. In addition, colorectal cancer risk assessment tools are available online which estimate an individual's 5 year, 10 year and lifetime risk of colorectal cancer based upon lifestyle and family history questions. This has the potential to either reassure individuals meaning that they don't seek formal assessment or alternatively may prompt them to pursue review.

Cairns et al. (2010) estimate that 750 individuals per population of 300,000 fulfil moderate risk criteria. This equates to 1181 individuals within the region of Cardiff and Vale alone, with an estimated population of 472,400 based upon census data (Cardiff and Vale UHB 2012). This demonstrates that only around a fifth of these patients has had contact with the medical genetics service for formal risk assessment and stratification. There is also a female preponderance of patients referred for genetic assessment (ratio 2.4:1.0), which is similar to previously published data (Holloway et al. 2005; Mak et al. 2007). This may be secondary to enhanced awareness of disease screening and surveillance due to other programmes including breast and cervical

screening. A higher uptake of FOB screening in women has also been reported by Bowel Screening Wales (Heard 2011).

Patients within the high-moderate risk group estimate a high lifetime risk of cancer (mean – 56.2%), with an apparent predominance in female respondents (Figure 23). It has been postulated that this overestimation results from a patient's lack of awareness that a genetic basis exists for only certain types of cancer, resulting in an increased perception of their personal risk (Phelps et al. 2004). It may also be that those seeking referral do so due to their perceived significant increased risk of cancer. The CGSW attempts to address concerns through a detailed risk assessment letter, which is personalised for each individual. It provides a summary of their family history information provided and confirmed, their risk stratification and recommended surveillance interval in addition to addressing any specific concerns or questions the patient has raised during their contact with the genetics service. This letter also discusses genetic inheritance, the population risk, possible aetiologies and alarm symptoms of colorectal cancer as well as potential opportunities for lifestyle modification. In addition, patients are offered the availability of a counsellor. This has been found to act as a source of reassurance in moderate risk patients (Hilgart et al. 2010). A locally published survey reported 80% of patients to be very or quite satisfied with their risk assessment letter and level of information provided (Phelps et al. 2004). However genetic counselling does not alter this level of perceived risk in addition to being less cost-effective (Griffith et al. 2005; Braithwaite et al. 2006; Metcalfe et al. 2009).

There was some variation in the advice provided regarding surveillance intervals, however five yearly surveillance was recommended to the majority of patients (93.8%),

which is consistent with updated national British Society of Gastroenterology (BSG) guidelines (Cairns et al. 2010). However it should be noted that this is more intensive surveillance than recommended in the previous BSG guidelines, which advised colonoscopy between the age of 35 – 40 years old or at the time of consultation and then repeated aged 55 years old (Dunlop 2002). 25.9% of individuals were advised to commence surveillance at a defined age. Local guidance recommends that the index colonoscopy be performed when the individual is five years younger than the youngest diagnosis of colorectal cancer in the family, taking into account the progression of adenomas through the adenoma-carcinoma sequence. Current BSG guidelines advise that surveillance commences at the age of 50 years old, due to the reported low prevalence of colorectal neoplasia below this age (Cairns et al. 2010). This corresponds to the largest age group category at the time of referral in our patient cohort (Table 11). 2.5% of individuals were advised to undergo a one off procedure in view of their older age.

It is current practice for surveillance recommendations to be sent to the referring physician following risk stratification. Therefore if the referral originates from primary care or a non-GI speciality team, additional correspondence is required to secondary care to arrange for colonoscopy (Table 13). 93% of patients referred from primary care or a non-GI speciality team have either undergone colonoscopy or been advised to commence surveillance at a future date. 4% of these patients have not been referred for colonoscopy, although it is not clear whether this is through patient choice or failure to act upon the recommendations provided. Although small in number, this represents a group of patients at increased risk of colorectal cancer above that of the general population and therefore a missed opportunity for adenoma detection. This study outlines some of the complex pathways that patients can follow from the point of initial

medical contact through to their surveillance procedure. A minimum of four referral stages are seen in 6.2% of referrals, leading to potential delays in initiating surveillance, shown to be associated with increased patient anxiety (Hilgart et al. 2010). Whilst patients at a moderate family history risk of colorectal cancer often reach the same end point (i.e. surveillance colonoscopy), this study has identified significant inefficiencies in the current system, which could be addressed through a re-organisation of our genetic services. This includes referral of any patient requiring surveillance to a nominated lead gastrointestinal (GI) clinician at each hospital in South East Wales, with a copy of the risk assessment recommendations sent to the referring physician. This approach confers several key advantages:

- 1) A reduced waiting time for patients to commence surveillance, as a result of shorter referral pathways.
- 2) Surveillance recommendations provided by the regional genetics service are sent directly to the department undertaking the colonoscopic procedures. This information is currently only provided to the referring physician. As cancer genetics service records do not form part of a patients standard medical records, secondary care specialities are reliant upon accurate information provided in the referral letters from primary care to determine surveillance intervals. Modification of the existing referral pathway would ensure that patients are offered appropriately timed surveillance, minimising the potential for both under surveillance which can leave individuals at risk of delayed detection of colorectal pathology or over surveillance which unnecessarily exposes asymptomatic individuals to the risks of colonoscopy. Referrals received by specialist teams without mention of previous genetics assessment, resulted in re-referral to the genetics department for stratification in 3.3% of cases. However in our experience a larger proportion of cases require

correspondence with the cancer genetics department to clarify their surveillance recommendations. It is equally important that the genetics department receive accurate information regarding colonoscopic surveillance outcomes (i.e: phenotypic data), to allow any necessary amendments to surveillance recommendations.

3) Reduced amount of administration and referrals generated from primary care.

This approach however does assume that an individual's request for genetics assessment is to pursue surveillance. There would also be absence of discussion regarding the risks versus benefits of surveillance and assessment of an individual's fitness to undergo the procedure that is currently undertaken by primary care.

5. Colonoscopic surveillance outcomes in patients with a moderate family history risk of colorectal cancer.

5.1 Background

An individual's risk of colorectal cancer is influenced by several factors including a positive family history. Both a greater number of family members affected and their younger age at diagnosis increase this risk. The moderate risk group is a cohort of patients at increased risk of colorectal cancer above that of the general population, but who do not follow any clear Mendelian inheritance pattern as with high risk conditions such as hereditary non-polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP) and MUTYH-associated polyposis (MAP). Risk stratification is accordingly based upon an individual's family history \pm negative genetic studies. Colonoscopic surveillance provides an opportunity to identify and resect conventional adenomas and serrated polyps through polypectomy, thereby reducing the risk of colorectal cancer. The majority of patients categorised into the high-moderate risk group by our regional cancer genetics service (Cardiff) are usually advised to undergo five yearly colonoscopy (Chapter 4), unless any pathology detected determines otherwise. This is in keeping with national guidance (Cairns et al. 2010). In the absence of randomised controlled trials studying the outcome of different surveillance intervals, these guidelines are largely based around observational studies. This arbitrary time interval considers the progression of adenomas through the adenoma-carcinoma sequence with opportunity for interruption of this pathway. The outcome and benefit of surveillance procedures in this population remains uncertain.

5.2 Study aims

1. Determine the yield of colonoscopic surveillance procedures in the high-moderate family history risk group.
2. Determine the distribution of pathology located within the colon.
3. Study the influence of detected pathology upon surveillance intervals.

5.3 Ascertainment of cases and methodology

A retrospective review of prospectively accumulated data was performed. A search of the CANISC (Cancer Network Information System Cymru) database was used to identify patients defined at a high-moderate risk of colorectal cancer following assessment by the South East Wales regional cancer genetics service between 1st January 2000 and 1st January 2011. Due to the small number of cases (n = 3), patients at low-moderate risk were excluded from this study. Cases were cross-referenced with a local gastroenterology genetics database, which holds the details of any patient who has contact with the gastroenterology department due to a family history of colorectal cancer. Patients are eligible for referral to one of three regional cancer genetics centres if they fulfil all Wales consensus guidelines for individuals with a family history of cancer. These include individuals with one first degree relative diagnosed aged ≤ 45 years old; two first degree relatives or one first degree and one second degree relative on the same side of the family diagnosed at any age or three relatives all on the same side of the family of which one is a first degree relative. Following receipt of a detailed patient questionnaire recording their demographics and family history, genetics counsellors verify information where possible. Risk stratification is undertaken using these details. The surveillance strategy is confirmed at a genetics multi-disciplinary meeting involving counsellors and clinical geneticists. Patients stratified into average or high risk colorectal cancer groups (i.e. those with HNPCC, FAP, MAP) and patients

with inflammatory bowel disease were excluded from the study. All colonoscopy reports were obtained for each patient from their index procedure, through a combination of local endoscopy reporting systems and patient medical records. White light colonoscopy was performed as standard for all procedures. Histopathological data was obtained from local results reporting systems and pathology databases. Five yearly colonoscopy surveillance procedures were undertaken as standard, unless detected pathology determined otherwise, in accordance with national adenoma surveillance guidelines (Atkin and Saunders 2002; Cairns et al. 2010). Conventional adenomas were classified according to the degree of villous component, as defined by the WHO classification. Rectosigmoid hyperplastic polyps were excluded from data analysis due to their doubtful clinical significance, unless greater than 1cm in size or in the context of serrated polyposis syndrome. The proximal colon was classified as large bowel located proximal to the splenic flexure (caecum, ascending colon, transverse colon and splenic flexure) and the distal colon as large bowel located distal to the splenic flexure (descending colon, sigmoid colon and rectum). Advanced adenomas were defined as polyp's \geq 1cm in size, villous or with high grade dysplasia. The adenoma detection rate was calculated by dividing the number of procedures in which a minimum of one adenoma was detected by the total number of procedures performed. Statistical analysis was performed using SPSS version 20 software (IBM UK Ltd, Hampshire, UK). An unpaired t-test was used to compare the number of polyps identified in different colonic segments.

5.4 Results

Of 262 patients defined as high-moderate risk within the study period, 172 patients (129 female and 43 male) have undergone surveillance colonoscopy: 105 have had a single procedure, 51 patients two procedures and 16 patients three or more procedures. Caecal

intubation was achieved in 165 colonoscopy procedures (95.9%). Six patients were referred for completion barium enema and one patient for CT pneumocolon, which were all reported as normal.

The mean age at the index surveillance colonoscopy was 50.8 years old (range: 20 – 81 years old). 2.3% patients (n = 4) were under the age of 29, 9.3% (n = 16) in their 30's, 36.6% (n = 63) in their 40's, 30.2% (n = 52) in their 50's, 18.0% (n = 31) in their 60's, 2.9% (n = 5) in their 70's and 0.6% (n = 1) 80 or above. Some patients only underwent a one off procedure in view of their age.

A total of 58 polyps were identified overall: 40 conventional adenomas, 1 serrated adenoma and 17 hyperplastic polyps (proximal to the sigmoid-descending junction) (Table 14).

Site within the colon	TA number (median size - mm)	TVA number (median size - mm)	VA number (median size - mm)	SA number (median size - mm)	HP number (median size - mm)
Caecum	2 (3.5)	2 (27)	0	0	0
Ascending colon	10 (2.5)	0	0	0	5 (4)
Hepatic flexure	1 (2)	0	0	0	3 (2)
Transverse colon	6 (4)	0	0	0	6 (2.5)
Splenic flexure	2 (3.5)	0	0	0	0
Descending colon	3 (3)	0	0	0	3 (3)
Sigmoid colon	7 (3)	4 (12.5)	1 (35)	0	NA
Rectum colon	2 (3)	0	0	1 (4)	NA
Total	33	6	1	1	17

HP, hyperplastic polyp; NA, not applicable; SA, serrated adenoma; TA, tubular adenoma; TVA, tubulovillous adenoma; VA, villous adenoma

Table 14 Polyp location and size according to polyp type

The overall median adenoma size was 4mm (range: 2 – 50mm), with a median proximal hyperplastic polyp size of 3mm (range: 2 – 7mm). Twenty eight adenomas (68.3%) were \leq 4mm in size (diminutive), six adenomas (14.6%) were between 5 – 9mm, four adenomas (9.8%) were 10 - 19mm and three (7.3%) were \geq 20mm. Forty adenomas

(97.6%) were classified as having low grade dysplasia, and one adenoma high grade dysplasia (2.4%). The overall polyp detection rate in women was 16.7%, compared to 20.5% in men ($p > 0.05$). The age at diagnosis of the first polyp is described in Figure 24.

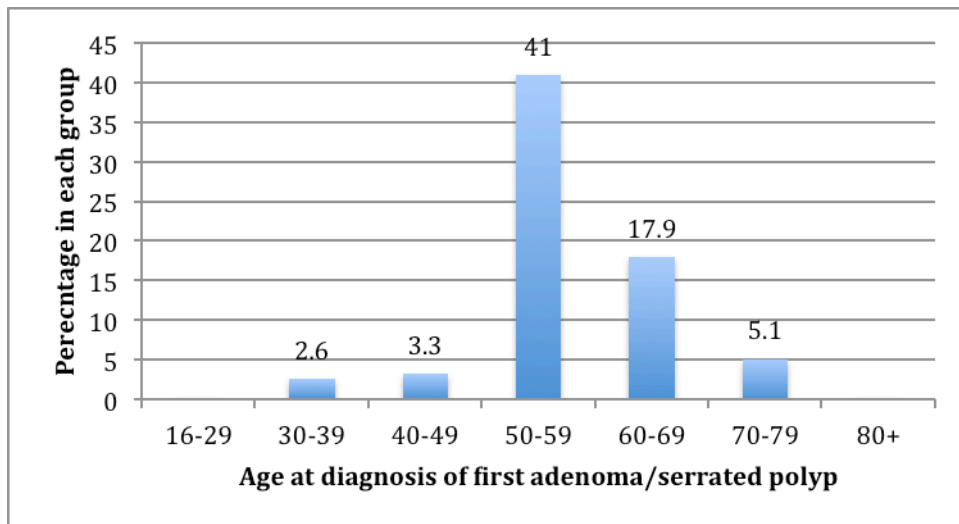


Figure 24 Age at diagnosis of first colorectal polyp

23 adenomas (23 conventional + 0 serrated) and 14 hyperplastic polyps were located in the proximal colon and 18 adenomas (17 conventional and 1 serrated) and 3 hyperplastic polyps were located in the distal colon (Figure 25). No significant difference was identified in the number of conventional adenomas located in the proximal versus distal colon, using a two-tailed chi-squared t-test ($X^2=2.23$; $p = 0.13$).

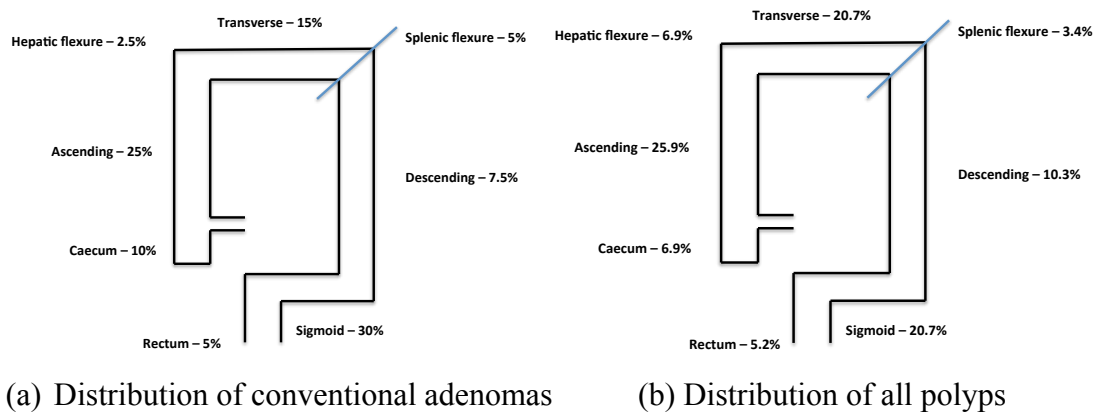


Figure 25 Distribution of colorectal pathology detected

Index surveillance colonoscopy

171 patients underwent an initial screening colonoscopy (1 patient was excluded due to a diagnosis of cancer made at a colonoscopy performed due to symptoms. Genetics risk stratification was performed at a later date). 155 patients were asymptomatic and 16 patients reported additional symptoms (12 rectal bleeding and 4 altered bowel habit). However no significant pathology was identified in the symptomatic group.

The adenoma (conventional + serrated) detection rate (ADR) was 11.1%, with a serrated (serrated adenoma + hyperplastic) polyp detection rate (SDR) of 8.2%. The detection rate for advanced adenomas was 4.1%. For individual's aged less than 50 years old, the ADR was 8.5% and SDR 7.3%. For those aged greater than 50 years old, the ADR was 13.5% and SDR 7.9%. The surveillance interval was increased from five to three yearly in 8 patients due to the findings at colonoscopy and in accordance with polyp surveillance guidelines (Cairns et al. 2010). One of these patients also underwent an interim sigmoidoscopy following removal of a 35mm sigmoid villous adenoma with high grade dysplasia.

Second surveillance procedure

A second procedure was performed in 67 patients:

- 11 out of 67 patients had at least one adenoma (ADR - 16.4%), of which 75% were located in the proximal colon. Of these 11 patients: 4 had a normal index colonoscopy and 7 had an adenomatous polyp detected.
- 2 out of 67 patients had a hyperplastic polyp (SDR - 3.0%), both located within the descending colon. Index colonoscopy was normal in both cases.
- No advanced adenomas were identified.
- No change in surveillance interval was required for any patient.

Third surveillance procedure

A third procedure was performed in 16 patients:

- 2 out of 16 patients had at least one adenoma (ADR - 12.5%), both located in the proximal colon. Both patients had a normal index and second surveillance colonoscopy.
- No patients had a proximal hyperplastic polyp or advanced adenoma detected.
- No change in surveillance interval was required for any patient.

Colorectal cancer risk and surgical intervention

One patient (0.6%) was diagnosed with Dukes C (T₃N₁M₀) ascending colonic adenocarcinoma aged 43 years old, after presenting with symptomatic iron deficiency anaemia and abdominal bloating. Subsequent risk stratification following diagnosis placed her into the high-moderate risk group. Follow up colonoscopy performed five years later, revealed a 3mm hyperplastic polyp located in the transverse colon. One other patient required a right hemicolectomy for a 50mm caecal laterally spreading tumour (LST), which was deemed endoscopically unresectable. Histology confirmed a

low grade tubulovillous adenoma. No interval cancers were observed during the period of the study.

5.5 Discussion

This study reviews the surveillance outcome of 255 colonoscopy procedures performed in patients stratified at a high-moderate family history risk of colorectal cancer by a regional cancer genetics service. Approximately two thirds (66.8%) of patients commenced colonoscopic surveillance between the ages of 40 - 59 years old. It should be noted that both the definition of the moderate risk group and recommended surveillance strategy was updated in national British Society of Gastroenterology guidelines in 2010 (Dunlop 2002; Cairns et al. 2010). However the all Wales consensus guidelines have remained consistent throughout this time period. There is additional variance with the surveillance recommendations provided, with regional advice being to commence surveillance in individuals at an age five years before than the youngest diagnosis of colorectal cancer in a family member. Whilst the polyp detection rate is highest in those commencing surveillance aged over 50 years old (Figure 24), future adherence to current national guidance would have resulted in a delay in adenoma (8.5%) and serrated (7.3%) lesion detection in those below this age. This includes a patient diagnosed with a 50mm caecal LST at the age of 48 years old, with reported rates of invasive cancer in such lesions of up to 10.3% (Tanaka et al. 2001). A minority of patients (3.5%) underwent a surveillance procedure aged over 70 years old. National guidelines advise to discontinue surveillance above the age of 75 years old due to the limited benefit in this age group (Cairns et al. 2010). However this should be discussed with each individual patient and in the context of any co-morbidity.

There is also a female preponderance of patients undergoing surveillance (Female:Male ratio of 3:1), which is in keeping with data reporting that females are more likely to seek risk stratification (Chapter 4). This may partly reflect better awareness through other screening programmes such as breast and cervical screening. Although not statistically significant, it should be noted that the polyp detection rate was higher in men than women (20.5% versus 16.7%; $p > 0.05$).

Of interest, are some of the phenotypic similarities that the moderate risk group have with HNPCC patients (Cao et al. 2002; Mecklin et al. 2007). 57.5% of conventional adenomas identified were located in the proximal colon, although this did not reach statistical significance when compared with the distal colon ($p = 0.13$) (Figure 25). The majority of adenomas identified were low risk, with low grade dysplasia (97.6%), less than 1cm in size (82.9%) and tubular in type (80.5%). However compared to HNPCC, the risk of colorectal cancer is greatly reduced (Lynch et al. 1985b; Mecklin et al. 2007). In this current study one patient (female) developed colorectal cancer (0.6%), which is comparable to previously published data (0.7 – 1.6%) (Dowling et al. 2000; Clark et al. 2003; Mak et al. 2007). Due to the low prevalence of cancer, it is not possible to draw any conclusions regarding location. This data emphasizes the importance of updating the medical genetics department with the outcome of colonoscopic surveillance procedures so that phenotypic information can be considered as a component of the risk stratification process.

The proximal location of pathology in this patient group highlights the need for meticulous high quality colonoscopy as the gold standard investigation, allowing resection of any polyps detected. Approximately 60% of colonic lesions would not have been detected at sigmoidoscopy alone. CT colonography is an alternative investigation.

However with a pooled ‘per patient sensitivity’ for polyps $\leq 5\text{mm}$ of 65% (95% CI 57 – 73%), it should ideally be reserved for those patients who have an incomplete colonoscopy (Sosna et al. 2003). Particularly due to the cumulative radiation exposure asymptomatic surveillance patients would otherwise receive.

There is limited data regarding surveillance outcomes in the moderate risk group. Adenoma detection rates in this study were 11.1% at the index procedure, which is comparable to the 14% reported by Mak et al. (2007). Bradshaw et al. (2003) reported a lower ADR of 4%. It should also be noted that one of the patients included had 12 adenomas, raising the possibility of a high risk syndrome such as MAP. The overall serrated polyp detection rate at index colonoscopy was 8.2%. However this is likely to be an underrepresentation, due to the advances in endoscopic technology and techniques such as high definition colonoscopy and more routine use of chromoendoscopy, and improvements in bowel preparation that may allow these often subtle lesions to be seen. Other factors such as operator technique and adequate withdrawal times may additionally influence polyp yield (Rex 2000; Barclay et al. 2006). There has also been an increased recognition of the importance of serrated lesions in recent years, as a pathway to proximal colonic cancer. An expert panel has published separate serrated polyp surveillance recommendations, but this area remains contentious (Rex et al. 2012).

As opposed to the high risk group in which there are well described genes that strongly correlate with an individual’s phenotype, the moderate risk group comprises a heterogeneous cohort of patients. In the absence of randomised controlled trials studying surveillance outcomes according to different time intervals, five yearly surveillance has been recommended in the most recent BSG guidelines based upon the potential evolution of adenomas to adenocarcinoma (Cairns et al. 2010). In this study,

all advanced adenomas were identified at the index surveillance colonoscopy, with none identified at subsequent follow up. The majority of patients with conventional adenomas (63.6%) identified at their second surveillance procedure had lesions identified at their index procedure, suggesting that there may be subgroups of patient who would benefit from more intensive colonoscopic surveillance. Recent genome wide studies have so far identified ten low-penetrance susceptibility genes that are likely to confer an additive risk of colorectal cancer in combination with environmental factors, but do not correspond to a specific phenotype (Tenesa and Dunlop 2009; Jasperson et al. 2010). There are currently no specific genetic markers available in clinical practice to identify higher risk patients within this group or in guiding surveillance intervals, which remain based upon an individuals family history. However future modelling may become available to distinguish those individuals at greater risk and who would benefit from more intensive surveillance (Dunlop et al. 2012).

With the propensity for proximal colonic pathology in this patient cohort, in the absence of adequate colonic cleansing a repeat or early procedure is advised. Future studies are required to evaluate the role of chromoendoscopy and other endoscopic imaging modalities in enhancing lesion detection, with increased yield reported in high risk groups.

6. Narrow band imaging in the surveillance of patients with a moderate family history risk of colorectal cancer.

6.1 Background

Surveillance colonoscopy is undertaken for a variety of indications including patients with a moderate or high family history risk of colorectal cancer and adenoma surveillance. With overall polyp miss rates of 22% with white light colonoscopy, endoscopic techniques have been sought to optimise polyp detection (van Rijn et al. 2006). Polyp detection rates may be influenced by a variety of factors including a family or personal history of colorectal cancer and polyps, as well as endoscopic factors such as the colonoscopists technique, withdrawal time and bowel preparation.

Narrow band imaging (NBI) reduces the bandwidth of white light to 415 and 540nm using a special filter located within the endoscope processor. These correspond to the absorption peaks of haemoglobin, thereby enhancing the vascular pattern of the mucosal surface (detailed description of NBI function is outlined in Chapter 1.6.2.1). Lesions undergoing neoplastic change are associated with the process of angiogenesis and increased prominence of the capillary patterns observed with NBI (Folkman 1971). NBI is a pre-processing technology, which can be easily activated through a push button on the control head of the colonoscope (Figure 26). Unlike chromoendoscopy it does not require any additional preparation time or equipment, resulting in a more efficient and less time consuming technique. This makes it an attractive modality for surveillance procedures. An initial study of patients within a high risk group showed increased polyp detection rates with NBI. East et al. (2008a) studied the proximal colon of 62 patients with HNPCC and reported a significant increase in adenomas detected from 25 with white light to 46 with NBI ($p < 0.001$). Adenoma detection rates of between 4 - 14%

have been reported in the moderate risk group, however the influence of NBI has not previously been studied. This study was undertaken to evaluate the role of NBI upon polyp detection during surveillance colonoscopy in this patient group.

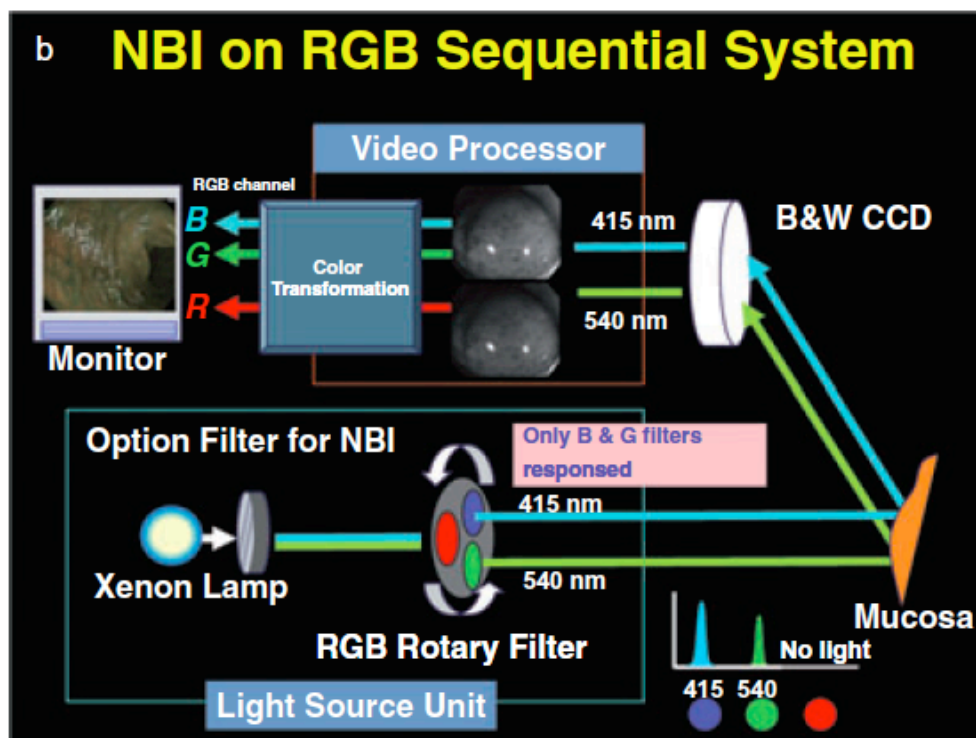


Figure 26 Diagram demonstrating the NBI imaging system (Reproduced from Muto et al. 2009).

6.2 Study aims

1. To determine the additional yield of colorectal pathology detected by NBI compared with high definition white light colonoscopy in patients undergoing colonoscopic surveillance for a high-moderate family history risk of colorectal cancer.
2. To ascertain the histology of colorectal pathology detected during surveillance colonoscopy during this study.

6.3 Methodology

6.3.1 Ascertainment of cases

Cases were recruited for the study prospectively, following referral to the gastroenterology department or endoscopy unit for colonoscopic surveillance due to a high-moderate family history risk of colorectal cancer. This included referrals from local gastroenterologists, colorectal surgeons, primary care and following risk stratification by our regional medical genetics service (Cardiff). Patients already involved in a colonoscopic surveillance programme for the same indication were also invited to participate.

The study inclusion criteria included patients with a high-moderate family history risk of colorectal cancer as defined by BSG guidelines and following risk stratification by the South Wales cancer genetics service (Table 2). The primary exclusion criteria were: (i) patients aged ≥ 60 years old, (ii) history of inflammatory bowel disease, (iii) personal history of colorectal cancer or previous colonic resection and (iv) patients within the average risk or high risk colorectal cancer group (eg: HNPCC, FAP or MAP). Secondary exclusion criteria were patients with an incomplete colonoscopy (i.e. those patients in whom the caecum was not reached) and those with inadequate bowel preparation. Patients in our endoscopy unit are categorised as having either excellent, adequate or inadequate bowel preparation.

Patients meeting the study inclusion criteria were invited to participate in the study. They were placed on dedicated family history colonoscopy lists, performed by the clinical research fellow (CRF) or consultant supervisor gastroenterologist in order to ensure standardised procedures as agreed between the two colonoscopists prior to commencing the study. Patients received 4 sachets of Klean prep (polyethylene glycol

3350 – Norgine Pharmaceuticals Ltd, Middlesex, UK) bowel preparation. Conscious sedation was offered with fentanyl and midazolam in line with BSG guidance (Teague 2003). All procedures were performed using an Olympus scope guide, with compatible CF H260 DL colonoscopes, which incorporate NBI. This was to aid localisation of the colonoscope during the withdrawal phase of the procedure. The caecal pole was confirmed by ileal intubation or identification of the ileocaecal valve, triradiate fold and appendiceal orifice. Intravenous Buscopan (20mg) was given at this point, unless contraindicated, to optimise mucosal visualisation during the withdrawal phase. Additional doses were given as required at the discretion of the endoscopist. The colonoscope was withdrawn from the caecum in a segmental approach. Patient position change was used to optimise mucosal visualisation during colonoscope withdrawal. The ascending colon was examined in the left lateral position, transverse colon supine and the left colon in the right lateral position if colonic distension was suboptimal. The colonoscope was initially withdrawn from the caecum to the hepatic flexure with inspection of the mucosa using high definition white light (segment 1). The hepatic flexure was identified using a combination of landmarks and configuration of the colonoscope on the scope guide. Any polyps identified were resected during this phase. The colonoscope was then reinserted to the caecum and withdrawn to the hepatic flexure using NBI. Any additional polyps that were identified were documented and removed during withdrawal. The NBI function could be turned off during polypectomy if required, but only following identification of pathology. The colon was then examined from the hepatic to sigmoid-descending (SD) junction using the same regime (segment 2). Any serrated or adenomatous polyps identified in segments 1 and 2 were deemed clinically significant and removed. The SD junction to the anal verge was then examined with white light alone (segment 3). Rectal retroflexion was performed as standard in all patients. Subcentimetre hyperplastic polyps identified in the rectosigmoid

colon were considered to be of no clinical relevance, however all other lesions were resected. A stopwatch was used to time the withdrawal time of each segment using a stopwatch by an independent assessor (endoscopy nurse). We aimed to use a minimum withdrawal time of 6 minutes for both the white light and NBI phases. Data was recorded on a standard proforma sheet (Appendix 2). All resected lesions were sent to the histopathology lab in 10% formalin for reporting. Polyp size was estimated using Radial Jaw 3 biopsy forceps (Boston Scientific, Natick, USA), with a closed diameter of 2.2mm and open diameter of 8mm. Future surveillance colonoscopy procedures were booked after considering recommendations from the medical genetics department and in accordance with BSG adenoma surveillance guidelines (Cairns et al. 2010).

6.3.2 Statistical analysis

Statistical analysis for the study was performed using SPSS version 20 software (IBM UK Ltd, Hampshire, UK). The average withdrawal times of segments 1 and 2 using high definition white light and NBI were compared using a paired t-test. The Wilcoxon signed rank test was used to study the additional yield of polyps detected by NBI compared with high definition white light, as the number of polyps detected did not follow a normal distribution. It was assumed that all polyps detected during the initial white light withdrawal phase would have also been detected by NBI. A p-value of < 0.05 was deemed as statistically significant.

6.3.3 Study approval

Cardiff and Vale NHS Trust provided Research and Development approval – project ID: 08/CMC/4347. Ethical approval was granted by the South East Wales Research Ethics Committee (Panel D) – reference number: 09/WSE04/11.

6.4 Results

45 patients agreed to participate in the study. Eight patients were excluded, as they did not fulfil the inclusion criteria (2 patients were classified as average or high risk of colorectal cancer, 2 patients had inadequate bowel preparation and 4 patients had either incomplete procedures or did not tolerate the increased procedure time required for this study secondary to discomfort). 37 patients (23 female; 14 male) were included in data analysis, with a mean age of 50.3 years old (range: 28 - 74). The mean total colonoscopy withdrawal time was 20.6 minutes (range: 9 – 49 minutes). There was no significant difference in the time taken to withdraw the colonoscopy from the caecal pole to the sigmoid-descending junction using white light compared with NBI ($p = 0.76$) – Table 15. No significant increase in polyp yield was identified with NBI compared to high definition white light colonoscopy ($p = 0.06$; 95% CI 0.008-0.208).

Case	Withdrawal time from caecum to SD junction – WL (seconds)	Withdrawal time from caecum to SD junction - NBI (seconds)	Number of polyps detected - WL	Additional number of polyps detected - NBI
1	145	164	0	0
2	105	141	0	0
3	169	159	0	0
4	360	372	0	0
5	410	390	1	2
6	367	368	0	0
7	395	390	0	1
8	376	387	2	0
9	214	309	0	0
10	355	351	0	0
11	303	310	1	0
12	350	379	0	0
13	304	233	1	0
14	306	315	0	0
15	300	299	1	0
16	246	253	2	0
17	302	247	0	0
18	240	256	0	0
19	285	344	1	1
20	487	326	2	1
21	292	309	0	0
22	310	315	0	0
23	261	278	0	0
24	261	260	0	0
25	305	310	0	0
26	286	287	0	0
27	237	226	0	0
28	257	229	1	0
29	320	324	0	0
30	208	136	0	0
31	228	215	0	0
32	296	232	0	0
33	227	260	0	0
34	320	325	1	0
35	264	236	3	0
36	321	284	1	0
37	219	222	1	0

SD, sigmoid-descending; **NBI**, narrow band imaging; **WL**, white light

Table 15 Colonoscopy withdrawal times and polyp yield during the NBI and white light withdrawal phases.

A total of 23 polyps were identified proximal to the sigmoid-descending junction (Table 16). The mean polyp size was 3.3mm (range: 2 – 7mm). Only one patient (case 28) had an adenomatous polyp (3mm low grade tubular adenoma) identified distal to the SD junction.

Modality	Histology (number of polyps)
White light	Hyperplastic – 3 Low grade traditional serrated adenoma – 1 Low grade tubular adenoma – 14
NBI	Low grade tubular adenoma - 5

NBI, narrow band imaging

Table 16 Polyp yield with each endoscopic modality (Segments 1 and 2)

6.5 Discussion

This is the first study that we are aware of to analyse the use of NBI in patients with a high-moderate family history risk of colorectal cancer. No significant increase in polyp yield was observed with NBI compared to high definition white light in this study ($p = 0.06$). However it should be noted that this value is close to being statistically significant, with wide confidence intervals, suggesting that the findings may have potentially been influenced by the small sample size. A randomised controlled trial would be required to validate these findings. Interestingly, similar findings have been reported in meta-analyses and systematic reviews of the average risk group since this study was undertaken (van den Broek et al. 2009a; Ng and Lau 2011; Dinesen et al. 2012; Jin et al. 2012; Nagorni et al. 2012; Pasha et al. 2012) (Table 17). However when compared with standard white light colonoscopy, high definition NBI is associated with lower polyp and adenoma miss rates (Gross et al. 2011). Limited studies of NBI in the high risk group have shown increased polyp detection in the proximal colon of patients with HNPCC and diminutive polyps in patients with FAP, compared with white light colonoscopy (East et al. 2008a; Matsumoto et al. 2009) (Table 17). However polyp

detection remains inferior when compared with other techniques such as chromoendoscopy (Huneburg et al. 2009; Matsumoto et al. 2009).

These findings may result from the darker endoscopic images that are obtained with NBI, with the colonic vasculature visible in green/dark brown (Figures 27 and 28) and residual stool as a red colour (Figure 29). Whilst all patients with suboptimal bowel cleansing were excluded from this study, in our experience even small amounts of residual stool can further degrade the images obtained with NBI compared to white light, limiting the potential to detect pathology. Inadequate bowel preparation is associated with higher adenoma miss rates in the proximal than distal colon, which is of particular importance due to the distribution of polyps identified in this patient group (Chokshi et al. 2012). It is interesting to note that all apart from one adenoma was located proximal to the sigmoid-descending junction, making it appropriate for colonoscopy rather than flexible sigmoidoscopy to be used as the most appropriate modality for surveillance of the moderate risk group.

The polyps identified in this study were small (< 1cm) low risk lesions (Table 16), which is consistent with our findings in a larger cohort of moderate risk patients (Chapter 5). Whilst not statistically significant, an additional total of five polyps were identified during the withdrawal phase with NBI. The adenoma detection rate in this study is 35.1%, which is higher than previously reported rates of between 4 – 14% (Bradshaw et al. 2003; Mak et al. 2007; Chapter 5). This suggests that the increased yield may have partly occurred due to a second viewing of the same colonic segment, particularly due to the small size of polyps detected (mean 3.3mm). A systematic review has reported a miss rate for diminutive polyps of 26% (van Rijn et al. 2006).

It has been hypothesised that use of NBI for adenoma detection may have a learning effect with a subsequent improvement in lesion recognition (Figures 30 and 31) with white light colonoscopy (Adler et al. 2008). Both operators in the current study were familiar with and regularly use NBI during their routine clinical practice. This was accordingly felt unlikely to have influenced our results. However one limitation of this study is its small sample size. As opposed to a randomised controlled trial, both modalities (high definition white light and NBI) were studied in the same patient, with the additional polyp yield being recorded. Due to this, a larger sample size was not required. Data collection was discontinued early following an interim statistical analysis that demonstrated no additional benefit with NBI in increasing polyp detection rates within this risk group. We also made the assumption that NBI would have detected all of the lesions identified during the initial white light withdrawal phase. Whilst there was variation in the total withdrawal times of the colonoscope from the caecum to the anus, the comparative times taken to examine each segment with white light and NBI were not significantly different ($p = 0.76$). This is therefore unlikely to have influenced the results of our study. It should be noted that this time included the time required to reinsert the colonoscope for re-examination of each segment.

This study demonstrates that NBI does not enhance polyp detection above high definition white light colonoscopy in patients with a high-moderate family history risk of colorectal cancer. However a previous study has suggested that it may confer a limited role in patients within the high risk group (East et al. 2008a).

Authors	Study design	Patient Number	Comparing	Results
Average risk group				
Rex and Helbig 2007	RCT	434	HDWL vs HDNBI	ADR: 67% vs 65% (p=0.61)
Adler et al. 2008	RCT	401	SWL vs NBI	ADR: 16.7% vs 22.7% (p=0.13)
Inoue et al. 2008	RCT	243	SWL vs NBI	ADR: 39% vs 51% (p=0.06)
Kaltenbach et al. 2008	Prospective back to back*	276	HDWL vs HDNBI	ADR: 44% vs 50% (p=0.29)
Adler et al. 2009	RCT	1256	HDWL vs HDNBI	ADR: 0.34 vs 0.32 (p>0.05)
Paggi et al. 2009	RCT	211	HDWL vs HDNBI	ADR: 58.3% vs 57.3% (p=0.69)
Gross et al. 2011	RCT	96	SWL vs HDNBI	AMR: 49% vs 27% (p=0.04)
Rastogi et al. 2011	RCT	630	SWL vs NBI	ADR: 38.6 vs 46.2 (p=0.14)
Sabbagh et al. 2011	RCT	482	HDWL vs HDNBI	PDR: 24.9% vs 20.8% (p>0.05)
Ikematsu et al. 2012	RCT	782	SWL vs NBI	ADR: 42.5% vs 42.4% (p=0.98) PDR: 47.6 vs 49.1 (p=0.67)
High risk groups				
HNPCC				
East et al. 2008	Prospective back to back*	62	HDWL vs NBI	AMR: 46%
Huneburg et al. 2009	Prospective back to back*	109	SWL vs Chro Chro vs HDNBI	ADR: SWL vs Chro = 7 vs 9 (p>0.05) ADR: Chro vs HDNBI = 22 vs 9 (p=0.04)
HPS				
Boparai et al. 2011	Prospective randomised crossover	22	HDWL vs NBI	AMR: 30% vs 0% (p=0.06) PMR: 36% vs 10% (p<0.001)
FAP				
Matsumoto et al. 2009	Prospective back to back*	13	SWL vs AFI vs NBI vs Chro	Total number lesions detected SWL vs NBI: 12.2 vs 20.1 (p=0.04) Chro vs NBI: 44.1 vs 20.1 (p=0.003)

*Back to back study design – initial withdrawal with one imaging modality followed by a different modality.

ADR, Adenoma Detection Rate; **AFI**, Autofluorescence Imaging; **AMR**, Adenoma Miss Rate; **Chro**, Chromoendoscopy; **FAP**, Familial Adenomatous Polyposis; **HDNBI**, High Definition Narrow Band Imaging; **HDWL**, High Definition White Light; **HNPCC**, Hereditary Nonpolyposis Colorectal Cancer; **HPS**, Hyperplastic Polyposis Syndrome; **NBI**, Narrow Band Imaging; **PDR**, Polyp Detection Rate; **RCT**, Randomised Controlled Trial; **PMR**, Polyp Miss Rate; **SWL**, Standard White Light.

Table 17 Narrow Band Imaging in the Detection of Colorectal Polyps

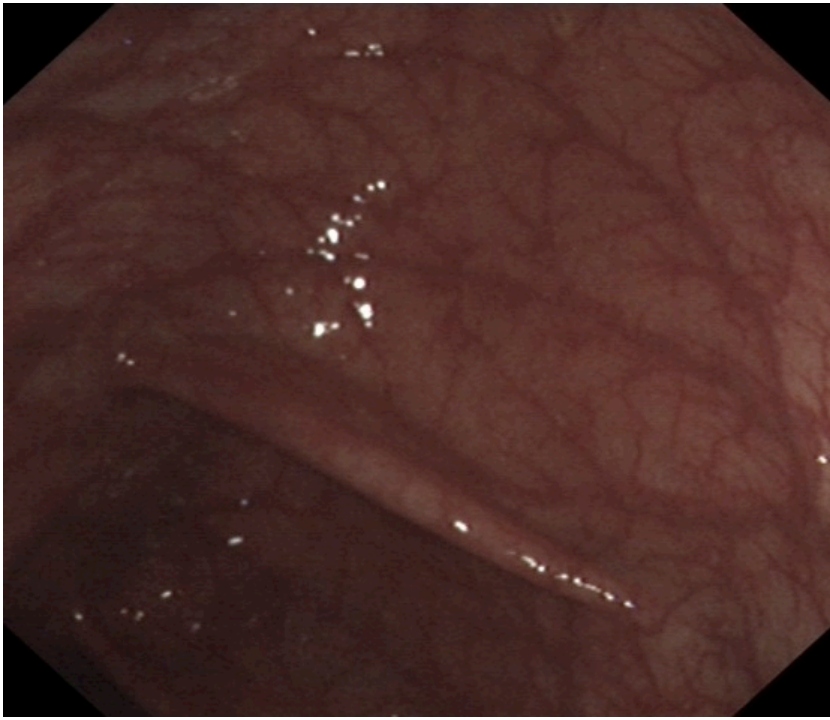


Figure 27 High definition white light image of normal colon.

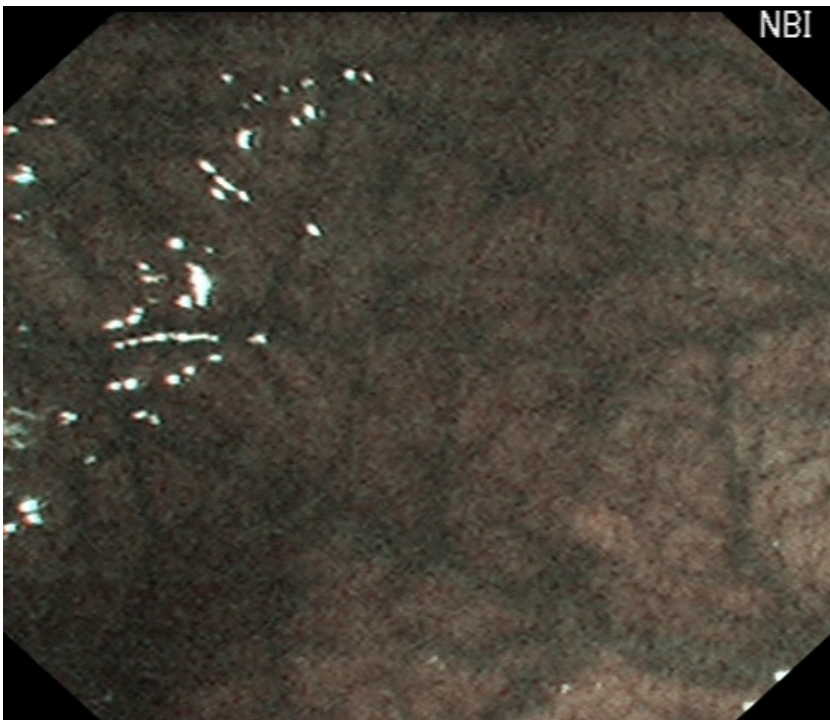


Figure 28 NBI image of normal colon.

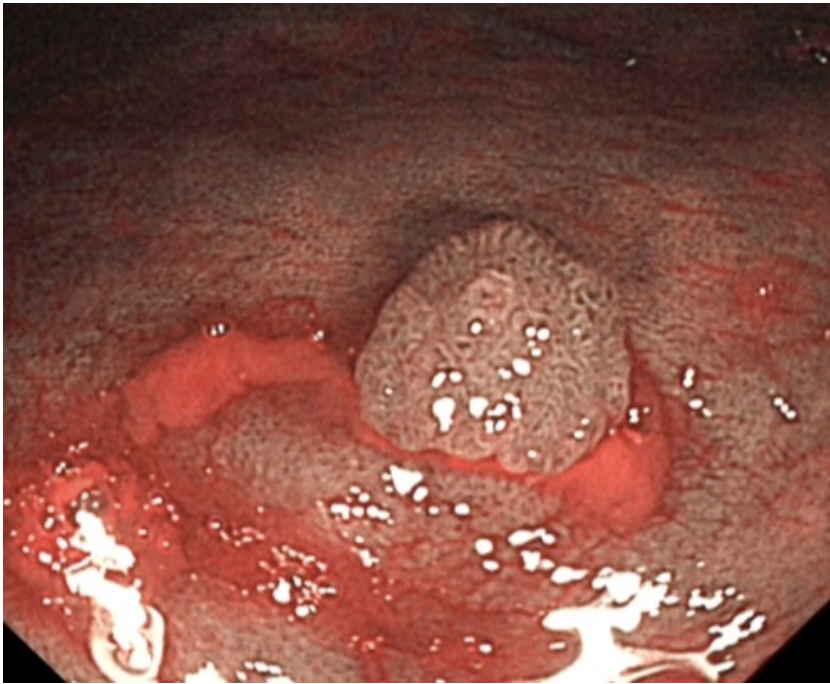


Figure 29 Small adenoma demonstrated using NBI (type II capillary pattern) with surrounding stool (red colour)

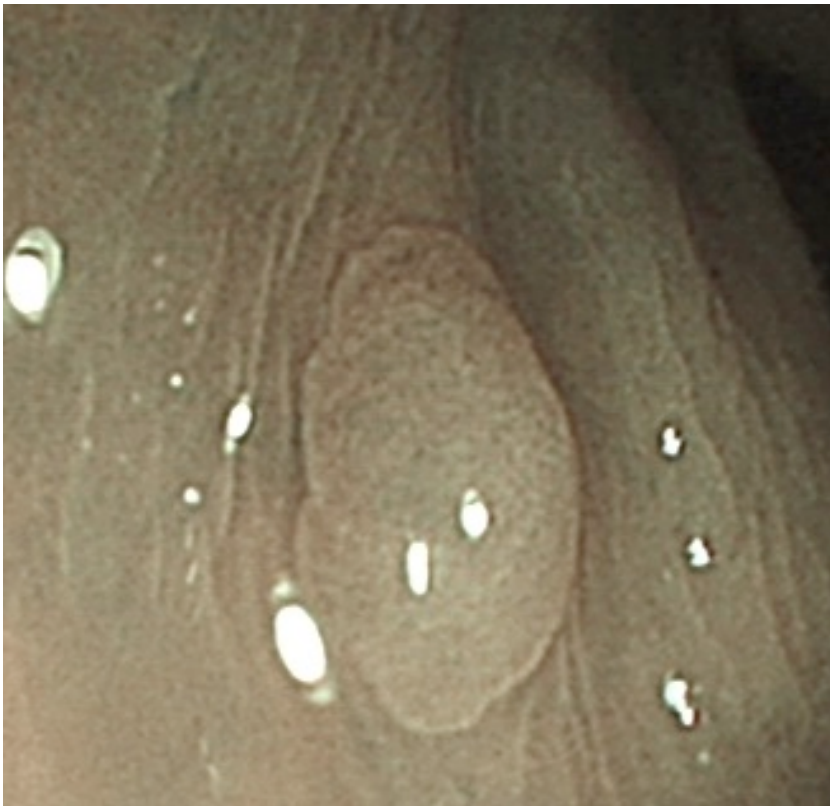


Figure 30 Hyperplastic polyp demonstrated using NBI (type I capillary pattern)



(a) White light view

(b) NBI view – type II capillary pattern

Figure 31 Adenoma demonstrated using white light and NBI imaging modalities

Chapter 7. Concluding discussion and future prospects

The moderate family history risk group consists of a heterogeneous cohort of individuals. The work presented has shown the majority of pathology detected at colonoscopic surveillance to include low risk adenomas. However there appears to be a subgroup of patients that would benefit from an enhanced surveillance strategy. The genome wide study has identified ten low-penetrance loci, providing further insight into the molecular aspects of colorectal cancer (Tenesa and Dunlop 2009). The development of risk models incorporating genotype data should help identify such patients (Dunlop et al. 2012). Existing definitions and surveillance strategies differ internationally, reflecting the paucity of data upon which they are based and varying interpretation by each group. There is a general move to try and standardise guidelines internationally as exist for some high risk groups (Vasen et al. 2008). Future studies are required to analyse the impact of different surveillance intervals upon polyp yield and outcome.

Whilst referral pathways are well developed within each speciality, additional work is required to streamline processes between departments such as the medical genetics service and endoscopy department, thereby improving efficiency and minimising the duplication of referrals. The existing genetics service is predominantly reactive, engaging individuals with an established family history of colorectal cancer. Future development of this service may include a more proactive approach with review of index cases of colorectal cancer. There is also a preponderance of women seeking risk assessment and stratification, suggesting that there is a group of at risk men not currently undergoing surveillance. Psychosocial studies are required to examine the reasons for this.

The impact of different endoscopic modalities upon polyp detection has been examined in patient groups at risk of polyp multiplicity, but with no prior studies looking at the moderate risk group. We have demonstrated that narrow band imaging does not significantly improve polyp yield above high definition white light colonoscopy. However with some phenotypic similarities to HNPCC, future studies are warranted to examine the potential role of chromoendoscopy, which has demonstrated additional benefit above NBI in this high risk group.

Polyp size in addition to multiplicity is required to determine appropriate future surveillance intervals in at risk patients. The work presented identified post-fixation measurements to result in less potential surveillance variability compared with in situ measurements. There is a need for further studies to determine the impact of different measurements upon outcome measures such as the subsequent risk of neoplasia. Through studying the interobserver agreement in the reporting of both common colorectal pathology and that posing diagnostic challenges, we were able to identify specific areas requiring further attention. These included the reporting of excision margin status of benign pathology and misinterpretation of high grade dysplasia in polyps with epithelial misplacement as adenocarcinoma, having the potential to significantly impact patient management. These areas could be addressed through more detailed histopathology guidelines, focused local and national study days and further development of e-learning modules.

Endoscopic imaging modalities are developing at a rapid pace, with the potential to enhance polyp detection and in situ assessment of detected colorectal pathology. Dual focus NBI has recently become commercially available (Olympus Medical systems, Japan). The depth of field visualised can be adjusted from a 'normal focus' to 'near

focus' mode using a push-button, allowing the prediction of colorectal histology with high accuracy (Singh et al. 2013). A second generation AFI system has also been developed with a noise reduction algorithm to enhance image quality, however future studies are required to assess its impact upon the visualisation of colorectal neoplasia. Fujinon (Japan) is currently developing an imaging modality named Blue Laser Imaging (BLI). BLI utilises two semi-conductor lasers as a light source, with wavelengths of 415 & 450nm. In addition to white light observation it incorporates a narrow band light function, without the requirement for an optical filter. Future studies are required to evaluate its effectiveness compared to existing technologies such as NBI, FICE and I-scan.

Molecular imaging techniques such as confocal endoscopy allow the real time visualisation of mucosal surfaces with immediate histological images and observation of the cellular and vascular networks. A low power blue laser delivers an excitation wavelength of 488nm, focused upon a specific section of tissue. Light from this point is then focused through a small hole to a detector. An image is created, representing a single focal plane. The illumination focus point and hole to the detector are focused upon the same point and are referred to as being confocal with each other. Several contrast agents are available to enhance the picture including intravenous 10% fluorescein solution which binds strongly to albumin, highlighting the blood vessels under laser stimulation, Acriflavine which is applied topically to label the mucosal cells and nuclei and cresyl violet (Kiesslich and Neurath 2007; Goetz et al. 2009). Two systems are currently available including an endoscope incorporating a confocal endomicroscope (EC-3870 CIFK, Pentax, Japan) and a probe based laser endomicroscope (Cellvizio, Mauna Kea Technologies, France) that can be inserted down the accessory channel of the colonoscope. Neoplastic changes can be predicated

with a 97.4% sensitivity and 99.4% specificity when compared with histopathology (Kiesslich et al. 2004; Hurlstone et al. 2008). The evolution of such endoscopic technologies will continue to push the boundaries of polyp detection, benefiting patients at increased risk of colorectal cancer.

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Appendices

Appendix 1 Example histopathologist reporting sheets (Chapter 3).

Histopathologist reference number: 18

Slide number: 1
(please ensure that this number corresponds to the number on the slide)

Please tick the appropriate boxes (NB: only one box should be ticked per question):

Polyp type:

- Hyperplastic polyp []
- Serrated adenoma []
- Classical adenoma: Tubular []
Tubulovillous []
Villous []
- Adenocarcinoma []

Degree of dysplasia:

- No dysplasia []
- Low grade dysplasia []
- High grade dysplasia []

Completeness of histological excision:

- Lesion completely excised []
- Lesion **in**completely excised []
- Uncertain []

Any additional comments:

.....
.....
.....
.....
.....

Please refer to the National Bowel Cancer Screening Histopathology guidelines for reporting standards (www.cancerscreening.nhs.uk/bowel/publications/nhsbcsp01.pdf) & **report the most severe degree of dysplasia identified on the slide (where appropriate).**

Appendix 2 Template genetic risk assessment letters for the high-moderate risk group (Chapter 4).



Cardiff and Vale NHS Trust

Ymddiriedolaeth GIG

University Hospital of Wales
Ysbyty Athrofaol Cymru

Clinical Director: Dr. Annie Procter

Director of Laboratory Services: Dr. Ian Frayling

Directorate Manager: Mr. Andrew Crowder

Cancer Genetics Service for Wales Services Accommodation Centre

Dr. Alex Murray, Consultant Clinical Geneticist
Clinical Geneticist

Dr. Mark T. Rogers, Consultant

Our Ref:
NHS No:

Date

Confidential

Dear

Your doctor has asked us to assess your family history of cancer. Cancer occurs when some of the cells in the body become abnormal. It is a complex disease and usually develops gradually as a result of a variety of factors. These factors include the environment, our lifestyle and our genes.

Cancer can occur in several members of a family simply by chance alone. Most cancer (approximately 95%) is not due to an inherited factor since 1 in 3 people will develop cancer at some point in their lifetime. Bowel cancer occurs quite commonly in the general population with around 1 in 20 developing this cancer at sometime in their life. Only a small proportion of cancers involve inherited genes which are passed from generation to generation. Certain clues in a family history may help to identify those cancers which may be inherited. Some of these clues include the same cancer occurring in several individuals on the same side of the family, the age at which the cancers occur, certain combinations of cancers and the presence of rare cancers.

We have assessed your risk on the basis of the family history you have given. You have told us about

Since you have some family history your risk of developing bowel cancer is probably increased over and above the general population risk. We would therefore fit you into what we call our **moderate risk** group. This means that your risk of developing bowel cancer is increased over the general population levels but not enough to think that there could be a single gene fault causing a significantly increased risk of developing bowel cancer.

What does this mean?

We would currently recommend that you have a colonoscopy at 5-yearly intervals. Colonoscopy is a process whereby the bowel is looked at via an instrument placed in the back passage. Although such screening does not prevent problems from happening it can detect any bowel changes at a very early stage. We have written to your GP and suggested that they refer you to the local Consultant Specialist so that this screening can be organised for you.

It is important to know what a normal bowel habit is for you and it is worth reporting any changes to your GP promptly. Some of the symptoms to look for include the presence of blood in the stool or faeces, persistent changes in bowel habit such as tending towards diarrhoea or constipation, or change in the colour of your stools that last for a few weeks or more. Other possible signs are a feeling of not completely emptying your bowel or passing mucus with your stools. However, it is important to remember that many of these symptoms are most often caused by problems much less serious, so try not to worry, but do get them checked out.

We understand that this letter may not answer all of your questions, so please do not hesitate to contact me on if you have any further questions or queries. We would be happy to review these findings at any time if anything changes in your family history. We would also be grateful if you would inform us of any change to your home or GP contact details. I will be sending a copy of this letter to your GP and any other doctors that may have referred you to us. Please allow 1-2 weeks for us to send this information back to your GP. You may wish to make an appointment to discuss things further with them.

With best wishes and kind regards

Yours sincerely

Cancer Genetic Counsellor (Macmillan)

Copy to:

GP/Referrer

Appendix 3 NBI colonoscopy study data collection proforma sheet
(Chapter 6).

Patient Sticker:

Colonoscopy date:

Colonoscopist: JT
 SD

Type of bowel preparation: Klean prep No sachets taken:

Picolax

Grade of bowel preparation: Excellent
 Adequate
 Inadequate

Medication given during procedure:

Midazolam: mg
Fentanyl: mg
Buscopan: mg
Glucagon: mg
Peppermint oil enema:

Timings:

Time of anal intubation:

Time of caecal intubation:

Time of anal extubation:

Identification of caecal pole:

Ileocaecal valve
Ileal intubation
Triradiate fold
Appendiceal orifice

Withdrawal timings:

	Time for withdrawal
Caecum – hepatic flexure (white light)	
Caecum – hepatic flexure (NBI)	
Hepatic – splenic flexure (white light)	
Hepatic – splenic flexure (NBI)	
Splenic flexure – SD junction (white light)	
Splenic flexure – SD junction (NBI)	

Polyps detected:

Polyp No	Con/NBI	Polyp location	Endo polyp size (mm)	Paris class.	Kudo pit pattern	Capillary pattern	Biopsy	Snare	EMR
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									

If suspected malignancy:

Site:

Size: mm

Partially obstructing

Obstructing

Tattooed: Yes

No

Patient follow up:

OPD clinic weeks/months

Repeat procedure months/years

- Surveillance
- Poor bowel prep
- Planned EMR
- Other

Refer to surgeons

Refer to genetics

Arrange further investigation

- Incomplete procedure
- CT abdomen
- MRI
- EUS

Barium enema

Publications and presentations relating to this work

Publications

Turner, J.K. et al. 2013. A prospective study of the accuracy and concordance between in-situ and post fixation measurements of colorectal polyp size and their potential impact upon surveillance. *Eur J Gastroenterol Hepatol* 25(5), pp. 562-567.

Turner, J.K. et al. 2013. Interobserver agreement in the reporting of colorectal polyp pathology among Bowel Cancer Screening pathologists in Wales. *Histopathology* 62(6), pp. 916-924.

Turner, J. et al. 2010. Use of gelofusine for endoscopic mucosal resection. *Gut* 59(10), pp. 1446-1447.

Turner, J. et al. 2008. Stents and stentability: treatment for malignant bowel obstruction. *Br J Hosp Med (Lond)* 69(12), pp. 676-680.

Oral Presentations

Turner J. '*Genetic and histopathological factors affecting polyp surveillance*'.

Oral presentation at a British Society of Gastroenterology Satellite Symposium, ICC, Birmingham 2008.

Turner J, Green J, Dolwani S, Swift J. '*Stents and Stentability*'.

Oral presentation at the Welsh Association for Gastroenterology and Endoscopy, Metropole Hotel, Llandrindod Wells 2008.

Turner J, Dolwani S. '*A Teaching hospital experience of Endoscopic Mucosal Resection*'.

Oral presentation at the Welsh Association for Gastroenterology and Endoscopy, Metropole Hotel, Llandrindod Wells 2008. **(Prize awarded for the best oral presentation).**

Turner J, Dolwani S. '*Referral pathways and colonoscopic outcomes in 200 patients with a moderate risk family history of colorectal cancer*'.

Oral presentation at the Welsh Association for Gastroenterology and Endoscopy, Metropole Hotel, Llandrindod Wells 2009.

Poster Presentations

Turner J, Wright M, Morgan RM, Williams GT, Dolwani S. *'Polyp size measurements in the Bowel Cancer Screening Programme'*.

Digestive Diseases Foundation (DDF) conference, Liverpool, June 2012.

Turner J, Torkington J, Davies MM, Dolwani S. *'Laparoscopic assisted endoscopic mucosal resection'*.

Digestive Diseases Foundation (DDF) conference, Liverpool, June 2012.

Turner J, Dolwani S. *'The role of prophylactic clips in endoscopic mucosal resection'*.

Digestive Diseases Week (DDW) conference, Chicago, May 2009.

Turner J, Dolwani S. *'A teaching hospital experience of endoscopic mucosal resection'*.

Falk Symposium 166, Mainz, September 2008.