AN INVESTIGATION INTO THE IMPACT OF SCREENING ON TUMOUR AND HOST DETERMINANTS OF OUTCOME IN COLORECTAL CANCER

BY

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Abstract

Colorectal cancer is the third most common cancer and the second most common cause of cancer death in the UK. Outcome is directly related to stage at diagnosis with over 90% of patients with Stage I disease surviving their disease to 5 years compared to less than 10% of those with Stage IV disease. Symptoms for colorectal cancer can be non-specific, particularly when the disease is at its early stage, and hence screening has been introduced. Population screening in the UK, using faecal occult blood testing (FOBt) has been introduced over the past 10 years following several major randomized control trials and a Cochrane review that has shown improved cancer specific mortality in the region of 15% in those individuals invited. This has been attributed to the detection of early stage disease with around 50% of all tumours detected through screening being Stage I.

However, it has previously been shown that there are additional tumour and host prognostic factors outside of stage that can determine outcome. For example, the presence of venous invasion and the presence of an elevated host systemic inflammatory response have been associated with poorer cancer specific survival. These additional factors have not previously been studied within the context of a population screening programme or indeed within early stage disease. Moreover, the FOBt screening programme itself is not without its pitfalls. Uptake of the test is below that of other established cancer screening programmes and it is recognised that repeated screening rounds are required to achieve an acceptable sensitivity of the test.

This thesis sought to examine the first round of the Scottish Bowel Screening Programme within the West of Scotland and assess its effect on tumour and host determinants of outcome. In Chapter 1 an overview of colorectal cancer and current determinants of outcome is provided. In addition, colorectal cancer screening is explored in detail

including the evidence behind the current screening programme. Chapter 2 presents original data, utilising population databases, examining the changes in mode, site and stage of presentation across the West of Scotland that have accompanied the introduction of the national screening programme. It identifies that within non-metastatic disease there has been a shift towards a higher proportion of Stage I disease being present following screening introduction. Chapter 3 presents a detailed examination of the first round of screening in NHS Greater Glasgow & Clyde (NHS GG&C) emphasising the importance of the impact of deprivation throughout the screening programme. For example, deprived patients were less likely to take part, more likely to test positive, less likely to proceed to colonscopy following a positive test and less likely to have cancer detected at colonoscopy following a positive test.

Chapters 4, 5 and 6 utilise an original dataset of over 4000 patients who underwent colonoscopy following a positive test in the first round of screening in NHS GG&C generated through work from Chapter 3. Firstly, in Chapter 4, a theoretical model proposing a flexible sigmoidoscopy as a first line test, rather than a colonoscopy, is examined. It found a missed cancer rate of 17% and that around a third would require a completion colonoscopy, concluding that this would not be a desirable change to the current screening algorithm. Chapter 5 then examines the importance of potentially chemopreventative medications such as statins and aspirin, on the risk of neoplasia at colonoscopy, determining that patients on such medications did indeed have lower rates of neoplasia, significant neoplasia and cancer than those not on them. Chapter 6 then looks at symptoms in this population, identifying that around 40% had at least one bowel symptom however that these correlated poorly with the risk of significant neoplasia at colonoscopy. Chapter 7 explores outcomes in those who were invited but did not have a screen-detected cancer in order to examine the incidence of interval cancers (colorectal cancer within 2 years of a negative FOBt) and cancers in non-responders. Overall it identified a 30%

interval cancer rate. The chapter then explores differences in tumour and host factors between screen-detected and non screen-detected disease reporting that stage for stage, patients with non screen-detected disease had higher rates of systemic inflammation. Furthermore it characterises the similarity between interval and non-responder tumours suggesting that rather than representing biologically more aggressive tumours, interval cancers arise due to limitations of the test itself. Chapter 8 presents long-term outcomes in patients who have undergone a resection for Stage I disease prior to the introduction of screening. The results report an excellent 5-year cancer specific survival of 95% however an overall survival of 76%. It identifies the presence of an elevated pre-operative host inflammatory response as being associated with a worse overall outcome.

Tissue work exploring the local immune-cell microenvironment of both early stage and pre-malignant disease is the focus for Chapters 9 and 10. This characterisation of immune cell infiltrate identifies similar rates of peritumoural inflammation between T1 and T2 disease and validates a previously published automated scoring system. When exploring local inflammation within premalignant polyps there appears to be a change from low-grade to high-grade dysplasia signifying a specific response to early disease progression suggesting host immunosurveillance. Chapter 11 summarises the main findings of the thesis and presents future directions.

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Author's Declaration

The work presented in this thesis was undertaken between 2011 and 2015 in the Academic Unit of Colorectal Surgery at Glasgow Royal Infirmary. I declare that the work presented herein was undertaken by myself, except where indicated below:

- Assistance with data collection was provided by Dr Yasmin Grant (Chapter 3, 4, 5 and 6), Ms Erin McIlveen (Chapter 7) and Mr Arfon Powell (Chapter 8).

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Publications

The work presented in this thesis has resulted in the following publications:

- **Long-term follow-up of patients undergoing resection of TNM Stage I colorectal cancer: An analysis of tumour and host determinants of outcome**
  Mansouri D, Powell A, Park JH, McMillan DC, Horgan PG.
  World J Surg 2016 (Article accepted not yet in print)

- **A comparison of tumour and host prognostic factors in screen-detected versus non screen-detected colorectal cancer: a contemporaneous study**
  Mansouri D, McMillan DC, McIlveen E, Crighton EM, Morrison DS, Horgan PG.
  Colorectal Dis 2016 Feb (Epub ahead of print)

- **Temporal trends in mode, site and stage of presentation with the introduction of colorectal cancer screening: a decade of experience from the West of Scotland.**
  Mansouri D, McMillan DC, Crearie C, Morrison DS, Crighton EM, Horgan PG.
  Br J Cancer 2015 Jul;113(3):556-61

- **Flexible sigmoidoscopy following a positive faecal occult blood test within a bowel screening programme may reduce the detection of neoplasia.**
  Mansouri D, McMillan DC, Roxburgh CS, Moug SJ, Crighton EM, Horgan PG.
  Colorectal Dis. 2013 Nov;15(11):1375-81.

- **Comment on Luo et al.: Diabetes mellitus and the incidence and mortality of colorectal cancer: a meta-analysis of 24 cohort studies**.
  Mansouri D, McMillan DC, Crighton EM, Horgan PG.
  Colorectal Dis. 2013 Aug;15(8):1045.

- **The impact of aspirin, statins and ACE-inhibitors on the presentation of colorectal neoplasia in a colorectal cancer screening programme**.
  Mansouri D, McMillan DC, Roxburgh CS, Crighton EM, Horgan PG.
  Br J Cancer. 2013 Jul;109(1):249-56.

- **The impact of age, sex and socioeconomic deprivation on outcomes in a colorectal cancer screening programme.**
  Mansouri D, McMillan DC, Grant Y, Crighton EM, Horgan PG.
  PLoS One. 2013 Jun;8(6):e66063.

- **Screening for colorectal cancer: What is the impact on the determinants of outcome?**
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Presentations

The work presented in this thesis has resulted in the following presentations:

- **Temporal trends in colorectal cancer stage and presentation since the introduction of a national bowel screening programme**
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- **Changes in the inflammatory microenvironment in pre-malignant colonic adenomatous polyps: Evidence for immunosurveillance?**
  American Society of Clinical Oncology – GI Symposium, San Francisco *(Jan 15) – poster presentation*

- **Long term outcomes in Dukes A Colorectal Cancer: Analysis of tumour and host prognostic factors**
  Association of Surgeons of Great Britain & Ireland Annual Conference, Harrogate *(May 14) – oral presentation*

- **Efficacy of a population based colorectal cancer screening programme and analysis of outcomes in screen-detected and non screen-detected tumours**
  American Society of Clinical Oncology – GI Symposium, San Francisco *(Jan 14) – poster presentation*

- **Determinants of anaemia in screen-detected Colorectal Cancer**
  American Society of Clinical Oncology – GI Symposium, San Francisco *(Jan 14) – poster presentation*

- **Screening the worried well: Symptomatic individuals are less likely to have significant neoplasia at colonoscopy following a positive colorectal cancer screening test**
  Digestive Diseases Week, Orlando *(May 13) – poster presentation*

- **A comparison of tumour and host determinants of outcome in screen-detected versus non screen-detected colorectal cancer; a contemporaneous study**
  Digestive Diseases Week, Orlando *(May 13) – poster presentation*

- **Is there an indication for upper gastrointestinal investigation in faecal test positive but colonoscopy negative patients within a national bowel screening programme?**
  Association of Surgeons of Great Britain & Ireland Annual Conference, Glasgow *(May 13) – oral presentation*

- **The impact of aspirin and statin usage of an individuals risk of neoplasia within a colorectal cancer screening programme**
  American Society of Clinical Oncology – GI Symposium, San Francisco *(Jan 13) – poster presentation*

- **The impact of screening on tumour and host prognostic factors in colorectal cancer; a contemporaneous study**
  National Cancer & Research Institute Annual Conference, Liverpool *(Nov 12) – poster presentation*

- **The impact of age, sex and deprivation on outcomes within a colorectal cancer screening programme**
  American Society of Clinical Oncology Annual Conference, Chicago *(June 12) – poster presentation*

- **The use of flexible sigmoidoscopy in FOBt positive patients may significantly underestimate the risk of neoplasia**
  Association of Surgeons of Great Britain & Ireland Annual Conference, Liverpool *(May 12) - E-poster of distinction*

Definitions and Abbreviations

ACE-i:	Angiotensin-converting enzyme inhibitor
APR:	Abdomino-perineal resection
CEA:	Carcinoembryonic antigen
CRP:	C-reactive protein
CSS:	Cancer-specific survival
FAP:	Familial adenomatous polyposis syndrome
FIT:	Faecal immunochemical test
FOBt:	Faecal occult blood test (referring to any stool test design to detect haemoglobin or its break down products)
gFOBt	guaiac-based faecal occult blood test
HNPCC:	Hereditary non-polyposis colorectal cancer
INT:	Interval Cancer - Colorectal cancer within 2 years of a negative screening test
K-M:	Klintrup-Makinen score/grade
mGPS:	modified Glasgow prognostic score
MMR:	Mismatch repair gene
MSI:	Microsatellite instability
NA:	Non-attender for colonoscopy following a positive screening test
NHS GG&C:	NHS Greater Glasgow & Clyde - Healthboard
NICE:	National Institute for Health and Care Excellence
NLR:	Neutrophil to lymphocyte Ratio
NR:	Non-responder to screening invitation
NSD:	Non screen-detected colorectal cancer
OS:	Overall survival
SBoSP:	Scottish Bowel Screening Programme
SD:	Screen-detected colorectal cancer
SIGN:	Scottish Intercollegiate Guidelines Network
SIMD:	Scottish Index of Multiple Deprivation
SSPoCS:	Scottish Screen-detected Polyp Cancer Study
TME:	Total mesorectal excision
TNM:	Tumour, node, metastases
UC:	Ulcerative colitis
VELIPI:	Presence of either venous invasion, lymphatic invasion or perineural invasion

Dedication

To Michelle, who as girlfriend, fiancée and wife, has provided enduring support and encouragement throughout.

And to my parents, who have always stood by me and supported me in everything I have done.

1 INTRODUCTION

1.1 Colorectal Cancer

1.1.1 Epidemiology

Colorectal cancer has an estimated worldwide annual incidence of 1.2 million cases and is the third most common cancer in men and the second most common cancer in women. The highest incidence rates are in North America, Australia, New Zealand, Europe and Japan, with lowest rates in Africa and South central Asia (American Cancer Society 2011).

In the UK, colorectal cancer is the fourth most common cancer, and the third most common cancer in both males and females separately (Cancer Research UK). Annually, there are over 40, 000 new diagnoses accounting for 14% of all male cancer diagnoses and 11% of all female diagnoses. The overall incidence rate is rising, however this has been predominantly in males. In the UK, from 1975 to 2011, the European age-standardised incidence rate has risen from 45 per 100,000 to 58 per 100,000 in males, and from 35 per 100,000 to 38 per 100,000 in females (Cancer Research UK).

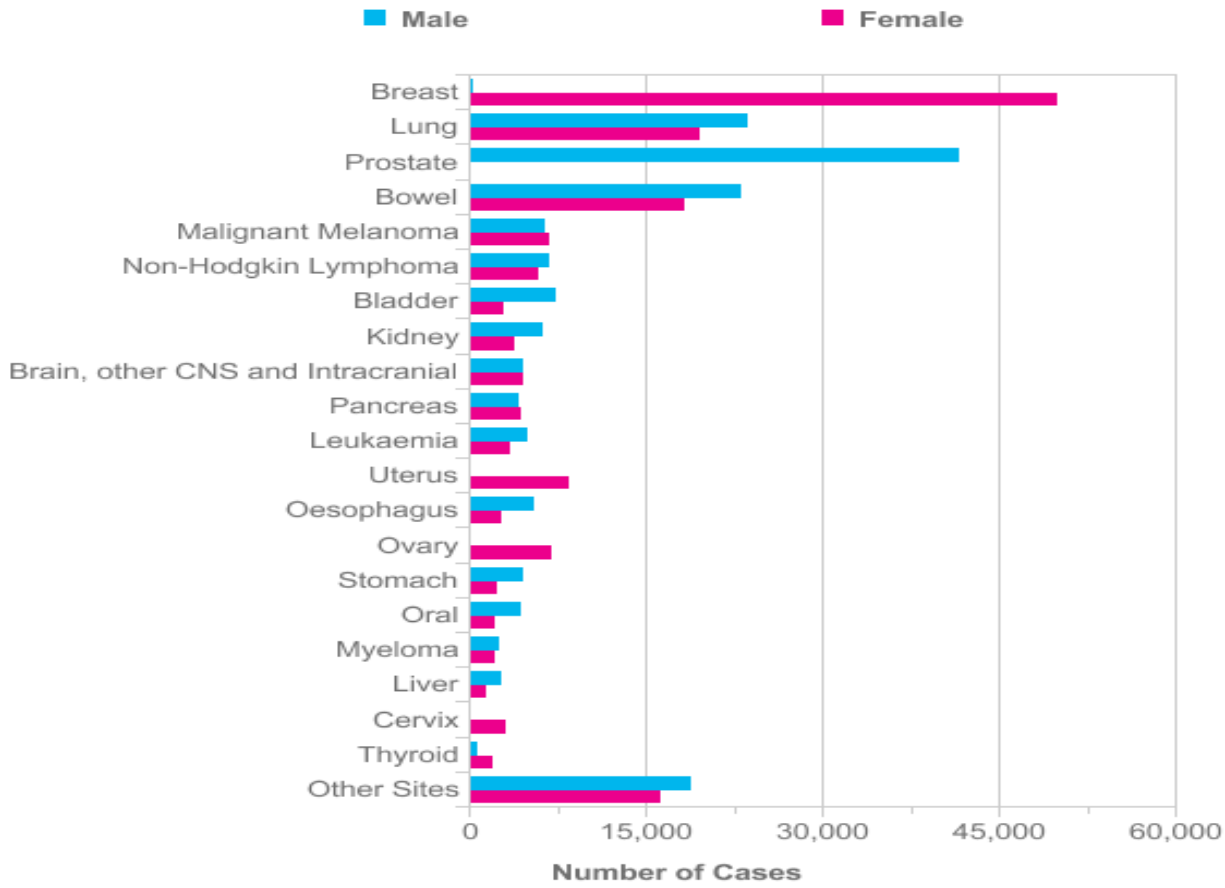


Figure 1.1: The 20 most common cancers in the UK

(reproduced Cancer Research UK)

1.1.2 Risk factors

The majority of cases of colorectal cancer are sporadic, arising on a background of genetic and epigenetic changes. There have been a variety of both modifiable and non-modifiable risk factors identified as being associated with an increased risk and will be discussed below.

1.1.2.1 Patient demographics

There are clear associations noted between patient age and sex and the development of colorectal cancer. In the UK alone, males have a lifetime risk of 1 in 14 of contracting the disease and females a risk of 1 in 19. Incidence increases with age, with a marked increase in incidence rate above the age of 50 years. It is estimated that 95% of cases occur in patients aged 50 or over (Cancer Research UK).

Socioeconomic deprivation is a global term used to describe an individual or group relative to the local community or wider society with regards to a variety of factors such as income, housing and education (Townsend 1987). There is evidence that those who are more deprived have higher rates of colorectal cancer, although more recently this has been shown to be a phenomenon that appears to only affect males (Oliphant, Brewster et al. 2011; Cancer Research UK). A recent study examining this within the West of Scotland suggested that cancer incidence rates were some 20% lower in males who were least deprived compared to the most deprived (Oliphant, Brewster et al. 2011). It is likely that the link between cancer risk and deprivation represents an overall assessment of a variety of modifiable risk factors associated with increased cancer risk that are associated with a deprivation.

1.1.2.2 Dietary and Lifestyle factors

There is evidence for a variety of both dietary and lifestyle factors to affect an individuals risk of colorectal cancer. In 2010, a large systematic literature review performed by the World Cancer Research Fund examined the current evidence available examining these factors and is summarised in Table 1.1 (World Cancer Research Fund 2010). The preventability of colorectal cancer through alterations of these lifestyle factors has been estimated at 28% in males and 15% in females in the UK alone (Parkin, Olsen et al. 2009). Key factors associated with risk will be discussed below.

1.1.2.2.1 Red and processed meat

Red meat (all fresh, minced and frozen beef, veal, pork and lamb) and processed meat (any meat preserved by methods other than freezing including marinating, smoking, salting, air drying or heating (including ham, bacon, sausages and tinned meat)) are associated with an increased risk of both colorectal cancer (Chan, Lau et al. 2011) and colorectal adenomata (Sinha, Kulldorff et al. 2001). This is thought to arise due to a direct effect on the local gut mucosa of several potentially carcinogenic compounds found in red and processed meat. These include heterocyclic amines and polycyclic aromatic hydrocarbons formed when frying meat (Ohgaki, Kusama et al. 1984), high haem-iron content of the meat (Tappel 2007), and endogenous formation of N-nitroso compounds (Cross, Pollock et al. 2003).

With regards colorectal cancer specifically, a recent meta-analysis has shown a relative risk of 1.22 when comparing those eating the lowest with those eating the highest amount of red or processed meat. This dose-response showed risk increasing up to 140g/day of intake, after which risk increase is less pronounced. Examining the risk of colorectal adenomas separately showed a similar summary risk 1.20 per 100g/day of red or processed meat ingested (Chan, Lau et al. 2011).

1.1.2.2.2 Dietary fibre

Dietary fibre is found in cereals, such as whole grains and vegetables. Diets high in fibre have been shown to be associated with a lower risk of colorectal cancer (Aune, Chan et al. 2011). The mechanisms explaining the link are thought to include increased stool bulk causing dilution of carcinogens in the colonic lumen, reduced colonic transit time and bacterial fermentation of fibre to short chain fatty acids which may have protective effects against colorectal cancer (Lipkin, Reddy et al. 1999). A recent meta-analysis found a dose response with increasing quantities of dietary fibre reduced colorectal cancer incidence (Aune, Chan et al. 2011). The summary relative risk for 10g of total daily dietary fibre was 0.93 with relative risk reductions also found when fibre subtypes were examined separately.

1.1.2.2.3 Physical activity

There is strong evidence that high levels of physical activity are associated with a reduced incidence of colon but not rectal cancer. The reasoning for this is likely to reflect the effect that regular exercise has on obesity and body fatness. In addition, physical activity reduces insulin resistance and insulin levels and has beneficial effects on lowering systemic inflammation which may further reduce risk (Harriss, Cable et al. 2007). A recent meta-analysis has estimated an inverse relationship with a relative risk of colon cancer of 0.80 in men and 0.86 in women in those who had increased leisure time physical activity (Harriss, Atkinson et al. 2009). A dose response was also seen across both genders adding further supportive evidence to this link.

1.1.2.2.4 Obesity

There is an overwhelming link between being overweight or obese and having a higher likelihood of a large number of cancers, including colorectal cancer (Harriss, Atkinson et

al. 2009). It has been proposed that overall obesity causes approximately 20% all cancers and 11% of all colorectal cancers (Cancer Research UK). The mechanisms for this are thought to be similar to those for sedentary lifestyle. This includes high insulin levels, high levels of circulating pro-inflammatory cytokines and higher levels of circulating sex hormones, all of which are associated with carcinogenesis (Giovannucci 2007; Giovannucci and Michaud 2007).

1.1.2.2.5 Alcohol intake

There is evidence to suggest that high levels of alcohol intake are associated with increased risk of colorectal cancer, particularly in males (World Cancer Research Fund 2010). In a meta-analysis of over 15 papers a 10% increase per 10g/day of alcohol ingested was found. This differed significantly between sexes with 11% in males and 7% in females. The precise mechanisms for the link between alcohol and colorectal cancer are unclear but may reflect carcinogenic metabolites of ethanol (World Cancer Research Fund 2010). In addition, those with higher alcohol levels are also more likely to have higher cumulative lifestyle risk factors as discussed above.

Table 1.1: Summary of dietary and lifestyle factors and risk of colorectal cancer
(adapted from World Cancer Research Fund 2010)

	Decreased Risk	Increased Risk
Convincing evidence	Physical activity Dietary fibre	Red meat Processed meat Alcoholic drinks (men) Body/abdominal fatness
Probable link	Garlic Milk Calcium	Alcoholic drinks (women)
Suggestive evidence	Non-starch vegetables Fruits Vitamin D	Foods containing Iron Cheese Animal fats Added sugars
Limited evidence – no conclusions	Fish; glycaemic index; folate; vitamin C; vitamin E; selenium; low fat; dietary pattern	

1.1.2.3 Pharmacological therapy

There is evidence, predominantly from observational studies, that a variety of commonly used medications are associated with a reduction in risk of colorectal cancer and as such could be considered as chemopreventative agents. The mechanism of action of these medications appears multifactorial and related to both systemic and local influences (Garcia-Albeniz and Chan 2011).

1.1.2.3.1 Aspirin and Non-steroidal anti-inflammatory drugs

The evidence for aspirin is perhaps the strongest of the proposed chemopreventative medications, as it has been shown to reduce the likelihood of developing both precancerous adenomas (Cole, Logan et al. 2009) and colorectal cancer (Flossmann and Rothwell 2007). It has been estimated that the reduction in risk of adenoma development is around 30% (Cole, Logan et al. 2009) and of colorectal cancer development around 26% (Cooper, Squires et al. 2010). This has been shown both *in vivo* and *in vitro* to be related to both a direct local effect on tumour cells and the tumour microenvironment and also a systemic effect on circulating cytokines (Garcia-Albeniz and Chan 2011). No clear evidence exists as to the optimal dose or duration and caution should be taken regarding the universal prescribing at a population level due to adverse effects such as gastrointestinal bleeding. However, there is now robust evidence that patients with hereditary cancers such as Hereditary Non-Polyposis Colorectal Cancer (HNPCC) or Familial Adenomatous Polyposis (FAP) may derive more substantial benefit form aspirin chemoprophylaxis (Burn, Bishop et al. 2011; Burn, Gerdes et al. 2011).

There is limited evidence for other non-steroidal anti-inflammatory drugs (NSAIDs) outwith selective COX-II inhibitors, which had been shown to reduce adenoma recurrence by 34% (Cooper, Squires et al. 2010). However, selective COX-II inhibitors are no longer

in clinical use due to the relatively high risk of adverse serious cardiovascular events such as stroke.

1.1.2.3.2 Statins

Hydroxylmethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also called statins, are commonly used medications that lower serum-cholesterol and are used to reduce cardiac morbidity and mortality. A large meta-analysis encompassing over a 2.5 million patients has shown that there is a modest effect on both colorectal cancer incidence of around 9% with statin usage, however no effect of adenoma development was seen (Bardou, Barkun et al. 2010). It has been proposed that statins exert their antitumour effect through induction of apoptosis, inhibition of cell growth or angiogenesis or enhancement of immune response (Gauthaman, Fong et al. 2009).

1.1.2.3.3 Angiotensin II converting enzyme – inhibitors

There is some evidence that Angiotensin II converting enzyme inhibitors (ACE-I) may have an effect on both colorectal cancer and adenoma development (Lever, Hole et al. 1998). It has been previously shown that ACE is present within colorectal adenomas and that by targeting this local tumour growth and neoangiogenesis may be arrested (Rocken, Neumann et al. 2007). Observational studies have found a reduction in advanced adenomas in users of ACE-I compared to non users estimated at 41% (Kedika, Patel et al. 2011), however direct evidence of an effect on colorectal cancer incidence is currently lacking.

1.1.2.3.4 Metformin

Metformin belongs to the biguanide class of agents and is the most commonly used drug in the treatment of type-2 diabetes mellitus (T2DM). Several observational studies have identified a reduced incidence of colorectal cancer in patients with diabetes who are being

treated with metformin (Libby, Donnelly et al. 2009; Lee, Hsu et al. 2011). This is likely due to both local effects on cell growth and proliferation, and systemic inhibitions of growth factors including insulin-like growth factor (IGF-1)(Belda-Iniesta, Pernia et al. 2011).

1.1.2.4 The systemic inflammatory response

Colotta et al (Colotta, Allavena et al. 2009) proposes that cancer-related inflammation is the seventh hallmark of cancer (Hanahan and Weinberg 2000) and that it is essential in causing activation of oncogenes and inactivation of oncosuppressors. It is recognised that an inflammatory component is present in the microenvironment of most neoplastic tissues, however, more recently, the systemic inflammatory response (SIR) has been identified as being a regulator of cancer progression and development (Box, Rogers et al. 2010).

C-reactive protein (CRP) is the prototypical marker of the SIR (Gabay and Kushner 1999). It is an acute phase protein that is elevated in response to several pathological conditions and diseases i.e. bacterial infections, sepsis, surgery, trauma, myocardial infarction inflammatory diseases and cancer. It is produced by hepatocytes under the control of cytokines (primarily interleukin-6) originating at the site of pathology. While bacterial and viral infections usually undergo a self-limiting acute phase response, some inflammatory agents will elicit a prolonged low-grade immune response that leads to a continuous, unresolved low-grade inflammation. It is this chronic state of low-grade inflammation that may predispose to malignant disease (Box, Rogers et al. 2010). In these cases CRP levels will be elevated and can be used as a measure of the magnitude of the SIR.

There is now good evidence that circulating levels of CRP are elevated in patients with cancer (Proctor, Talwar et al. 2010). Several epidemiology studies have examined the relevance of raised CRP in apparently healthy individuals and found it is associated with

an increased risk of cancer (Allin and Nordestgaard 2011). For example, Allin et al observed over 10 000 individuals in the Danish population and followed them up for 16 years after a baseline CRP level was measured. The risk of any cancer in individuals with a baseline CRP in the highest quintile was 1.3 times that of those with a baseline CRP protein in the lowest quintile (Allin, Bojesen et al. 2009). When colorectal cancer was examined independently from other cancers the association remained and this has been supported by other more recent work (Prizment, Anderson et al. 2011).

1.1.3 Aetiology

1.1.3.1 Sporadic colorectal cancer

The vast majority of colorectal cancers arise sporadically through the adenoma-carcinoma sequence. This model put forward by Vogelstein states that through a combination of genetic mutations adenomatous polyps develop and progress from low-grade to high-grade dysplasia changes to invasive malignancy (Vogelstein, Fearon et al. 1988). It is estimated that around a quarter of polyps greater than 10mm will develop into cancer over 20 years (Stryker, Wolff et al. 1987). Features in keeping with increased risk of malignant transformation in adenomas include size, sessile morphology and villous architecture (Hardy, Meltzer et al. 2000). Patients with colorectal adenomata are therefore recommended to undergo surveillance colonoscopy with current guidelines on frequency of examinations summarised in Figure 1.2 (Cairns, Scholefield et al. 2010). The genetic alterations driving sporadic colorectal cancer development are outlined in more detail in Section 1.1.3.3.

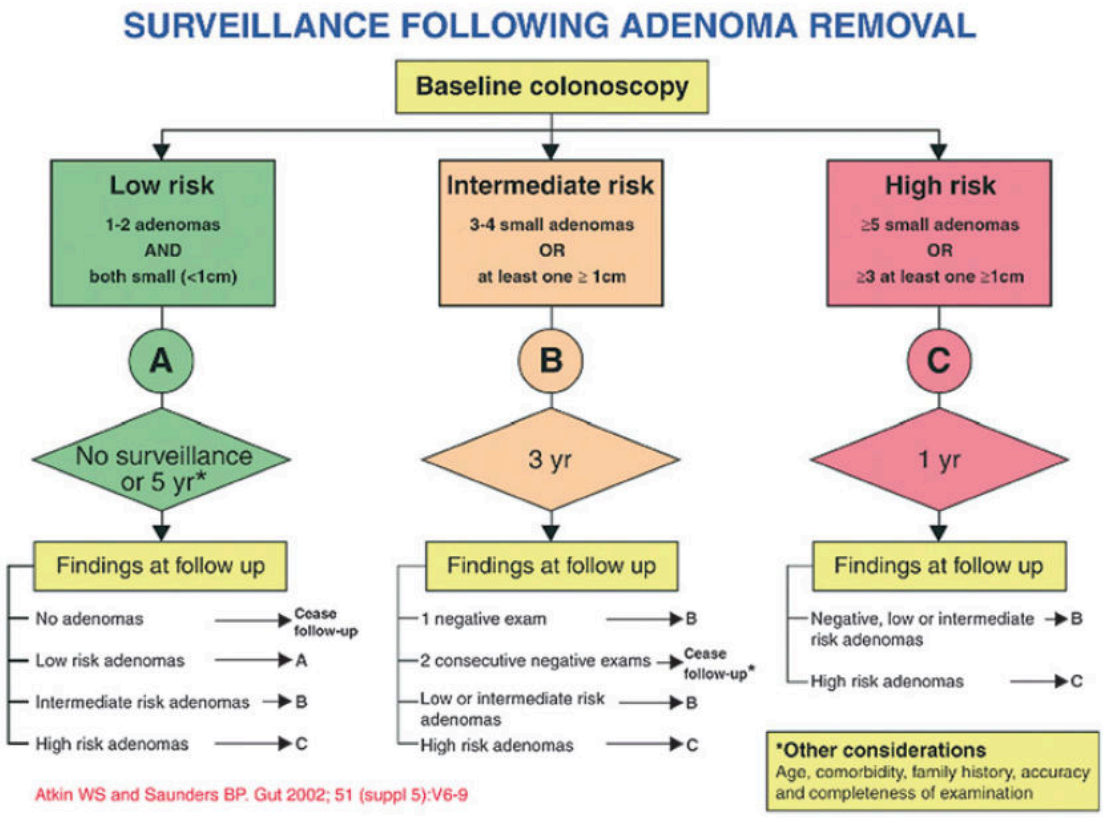


Figure 1.2: Surveillance guidelines after removal of adenomas

(Reproduced from Cairns et al 2010)

1.1.3.2 Non-sporadic colorectal cancer

Approximately 15% of colorectal cancers arise through non-sporadic routes either via inherited conditions or systemic diseases that pre-dispose individuals to the development of colorectal malignancy.

1.1.3.2.1 Hereditary Non-Polyposis Colon Cancer

Hereditary Non-Polyposis Colon Cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant genetic condition that is the most common of the inherited colorectal cancer conditions. Its incidence is approximately 1 in 3000 in the general population, accounts for approximately 1-2% of all colorectal cancer diagnoses and has an average age of onset of 45 years (Dunlop et al. 2002). It is characterised through mutation in DNA mismatch repair (MMR) genes leading to tumours with microsatellite instability (MSI). These tumours are predominantly right sided, patients have an increase risk of synchronous and metachronous tumours, and overall the disease has a better prognosis than colorectal cancers not arising through this pathway. Lynch syndrome is also associated with other cancers such as endometrial, gastric and urinary tract tumours (Vasen, Watson et al. 1999).

Not all MMR mutated tumours are due to HNPCC and therefore diagnosis can be difficult with genetic testing alone. The Amsterdam criteria, now modified to the Amsterdam II criteria, and the Bethesda criteria have therefore been developed to aid in diagnosis. The Amsterdam II criteria is based on family history and requires each of the following criteria required to be met: $\geq$3 relatives with colorectal or associated cancer; $\geq$2 successive generations affected; $\geq$1 relatives diagnosed before the age of 50 years; Familial Adenomatous Polyposis (FAP) syndrome excluded; and tumours verified by pathological examination (Vasen, Watson et al. 1999). The Bethesda guidelines identify patients who should undergo MMR genetic testing following a diagnosis of colorectal cancer and do not fit into the Amsterdam II criteria. They include any of the following: colorectal cancer in a

patient under 50 years; presence of synchronous or metachronous colorectal cancers; patient under the age of 60 years with microsatellite instability on histology; patient with colorectal cancer in ≥1 first degree relative with ≥1 under 50 years; or patient with colorectal cancer in ≥2 first or second degree relatives regardless of age (Umar, Boland et al. 2004). In patients meeting the Amsterdam II criteria the lifetime risk of colorectal cancer is approximately 80% (Vasen, Taal et al. 1995). In view of this, endoscopic surveillance with biennial colonoscopy is recommended from the age of 25 years or 5 years less than the first cancer case in the family and should continue until 75 years old (Dunlop et al. 2002). Following a diagnosis of colorectal cancer, there is a relatively high risk of a second cancer following partial colectomy. Therefore a full discussion of pros and cons of a subtotal colectomy should be discussed, this is particularly important with younger patients (Vasen, Watson et al. 1999).

1.1.3.2.2 Familial adenomatous polyposis syndrome

Familial adenomatous polyposis syndrome (FAP) is an autosomal dominant condition characterised by the development of multiple adenomas across the colon and rectum (Bulow 1989). The incidence in the general population is about 1 in 14 000 individuals and accounts for less than 1% of all colorectal cancers seen (Bulow, Bulow et al. 1995). It arises due to a germline mutation in the tumour suppressor gene adenomatous polyposis coli (APC), which is located on band 5q21. Loss of APC function leads to chromosomal instability and this affects proliferation, differentiation, migration and apoptosis of cells (van der Luijt, Khan et al. 1997). This ultimately allows hundreds to thousands of adenomatous polyps to develop across the colon and rectum all of which have malignant potential. The majority of patients are diagnosed in the second decade of their life and if not treated early then will develop colorectal cancer by their fourth decade. Diagnostic criteria is the presence of >100 polyps in the colon or rectum. The mainstay of treatment is endoscopic surveillance beginning in suspected individuals at age 13 and then prophylactic

colectomy in early adulthood. The treatment of choice is panproctocolectomy and ileoanal pouch, or permanent ileostomy, as rectal cancers can develop in those with rectum left in-situ. In those who do undergo colectomy and ileorectal anastomosis then endoscopic rectal surveillance is required at regular intervals (Dunlop, British Society for et al. 2002). In addition to the colonic manifestations, FAP is associated with extra-colonic malignancies such as desmoid tumours and upper gastrointestinal malignancies (Gurbuz, Giardiello et al. 1994).

An attenuated form of FAP (AFAP) is also now recognised. This is a milder phenotype characterised by the presence of 100 or less colorectal adenomas, a delay in onset of adenomatosis up to 20-25 years old, a delay in onset of colorectal cancer to 10-20 years old and ultimately a reduced risk of colorectal cancer (Knudsen, Bulow et al. 2010). Treatment and surveillance of these patients can be modified accordingly.

1.1.3.2.3 Inflammatory bowel disease

It is widely accepted that patients with inflammatory bowel disease (IBD), namely Ulcerative Colitis (UC) and colonic Crohn's disease have an increased risk of developing colorectal cancer (Devroede, Taylor et al. 1971; Ekbom, Helmick et al. 1990). The risk is associated with severity and duration of symptoms with figures derived from meta-analyses estimating risk in Crohn's disease at 3% at 10 years (Canavan, Abrams et al. 2006), and in UC at 2%, 8% and 18% after 10, 20 and 30 years respectively (Eaden, Abrams et al. 2001). It is hypothesised that chronic inflammation results in genetic alterations leading to the development of colonic dysplasia, which in turn can develop into invasive malignancy. As such, surveillance guidelines have been developed as summarised in Figure 1.3. All patients should have a screening colonoscopy at 10 years from duration of symptoms with subsequent scopes dependent on findings (Cairns, Scholefield et al. 2010).

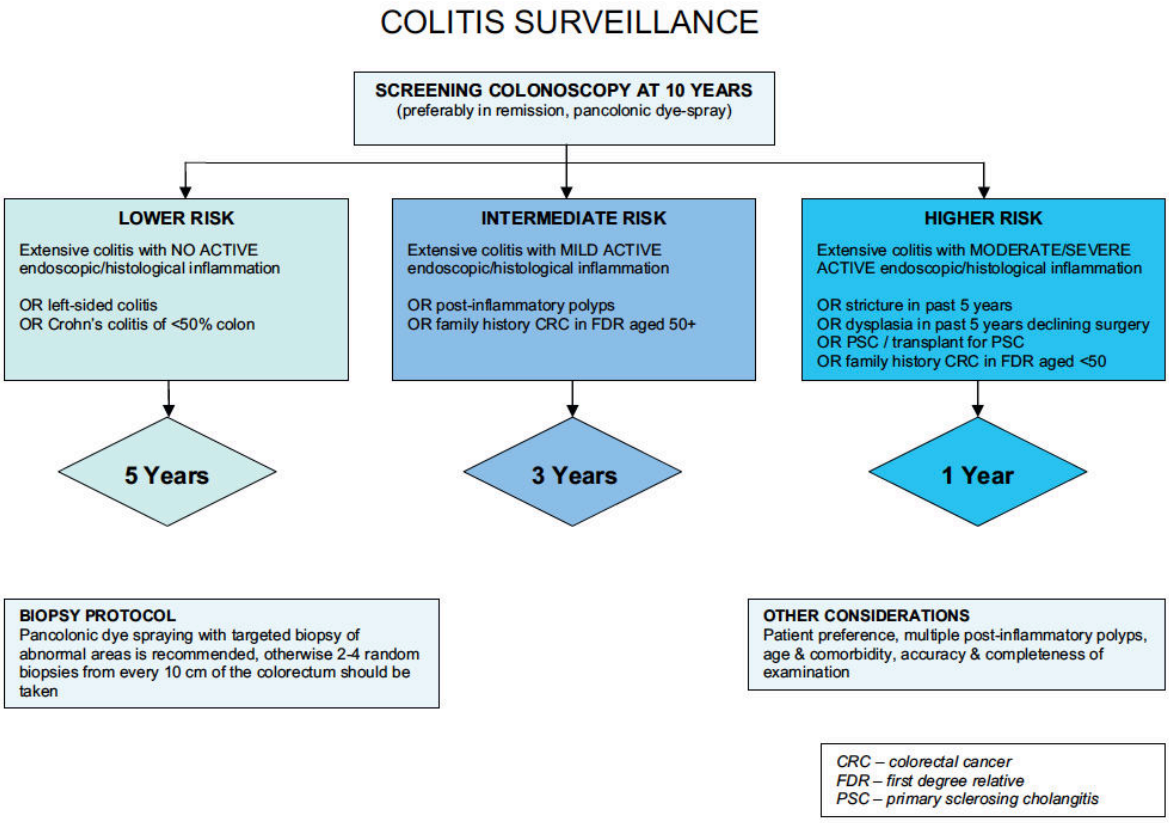


Figure 1.3: Surveillance guidelines for follow-up of colitis

(Reproduced from Cairns et al 2010)

1.1.3.3 Colorectal Carcinogenesis at a molecular level

Whether arising sporadically or non-sporadically there are several molecular pathways that have been implicated in the development and progression of colorectal cancer.

1.1.3.3.1 Chromosomal instability

The Vogelstein model of colorectal carcinogenesis proposed that a variety of genetic alterations at a local level led to the transformation of colonic mucosa to dysplastic adenoma and then into invasive malignancy (Vogelstein, Fearon et al. 1988). These genetic changes include alterations in chromosomal number (termed aneuploidy) and deletion of the APC gene. The original model of molecular changes in the adenoma-carcinoma sequence proposed that changes in oncogenes such as K-ras and ultimately mutation of p53 occurred in a stepwise manner, leading to invasive cancer (Figure 1.4). p53 is a DNA binding protein transcriptional activator and arrests the cell cycle in response to damage, however, mutations at the p53 gene locus cause the protein to become hyperstable and lead to its accumulation in the nucleus. This stepwise change in response to chromosomal instability is now thought to be an over simplistic representation of more complex process and that multiple oncogenes and tumour suppressor genes are responsible simultaneously (Wood, Parsons et al. 2007).

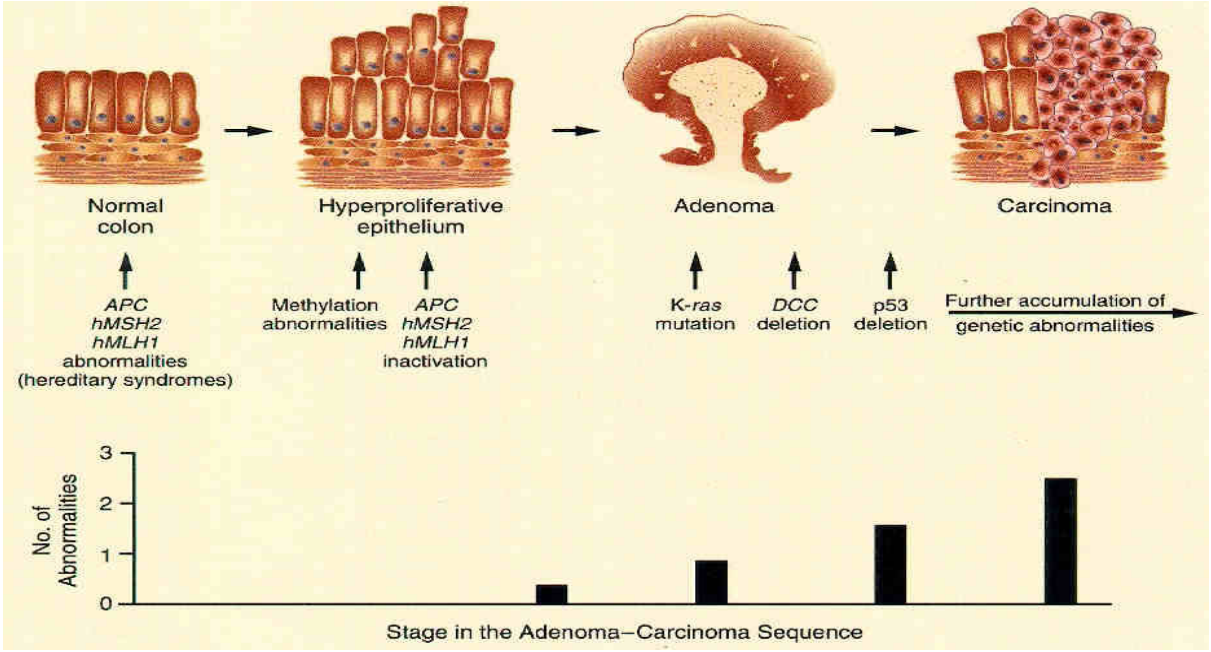


Figure 1.4: The adenoma-carcinoma sequence and accompanying molecular changes

(Reproduced from Toribara et al. 1995)

1.1.3.3.2 Microsatellite instability

Microsatellites are repeated sequences of DNA made up of repeating units of one to six base pairs that occur throughout the human genome. Due to their repetitive nature they are prone to changes during replication. Mutations in DNA mismatch repair genes (MMR) result in a failure to repair errors in repetitive sequences leading to microsatellite instability (MSI). This results in an accumulation of base pair mismatches (Boland and Goel 2010). The MSI pathway accounts for approximately 15% of all sporadic colorectal cancers however is closely linked to HNPCC, as discussed above. This occurs through two different mechanisms: in sporadic colorectal cancer epigenetic changes affect the MMR gene function without genetic changes per se; whereas in HNPCC there is a germline mutation in the MMR enzyme (Soreide, Janssen et al. 2006). Colorectal cancers with MSI tend to be right-sided and large, however have a better prognosis than other tumours (Soreide, Janssen et al. 2006).

1.1.3.3.3 DNA Hypermethylation

A third pathway has been described as being responsible for the development of colorectal cancer through epigenetic rather than genetic changes (Toyota, Ahuja et al. 1999). Aberrant DNA methylation, in the form of hypermethylation of CpG islands, results in repression of transcription of tumour suppressor genes. The presence of this within a tumour is termed the CpG island methylator phenotype (CIMP). CIMP positive tumours have certain characteristic clinicopathological features such as being right-sided, older age at diagnosis, female gender, poor differentiation, and have a high frequency of BRAF and K-ras mutations (Curtin, Slattery et al. 2011).

1.1.4 Diagnosis

1.1.4.1 Mode of presentation

Prior to the introduction of screening patients presented either electively or as an emergency and the majority were symptomatic. Mode of presentation is important as those that present as an emergency have a poorer outcome compared to those diagnosed and operated on electively.

A study by McArdle, looking at over 3000 patients diagnosed with colorectal cancer, identified that emergency patients were more likely to be older, female, with left sided lesions and with tumours of a higher stage and therefore more likely to have distant spread (McArdle and Hole 2004). Fewer of these patients who presented as an emergency were able to undergo curative resections and their 30-day post operative mortality was higher than the elective patients. In those that had potentially curative surgery, 5 year overall survival and 5 year cancer specific survival rates were significantly worse (58% and 71% in the patients presenting electively and 39% and 53% in the emergency patients, respectively). When the node-negative patients were examined separately, emergency presentation was still identified as being a negative prognostic indicator. A further study identified the individual components of emergency presentation that were important. When compared to those presenting electively, who had a 5-year cancer specific survival of 75%, blood loss (61% cancer specific survival), obstruction (52% cancer specific survival) and perforation (47% cancer specific survival) were all shown to be significant (McArdle, McMillan et al. 2006).

In the elective setting, the majority of patients present with three primary symptoms either in combination or isolation; rectal bleeding, change in bowel habit and abdominal pain (Keddie and Hargreaves 1968). Additional features that can lead to presentation in the elective setting include anaemia or a palpable mass. Identifying malignant from benign

causes of these symptoms is problematic however a previous study has examined age and symptom combinations to identify who is most at risk (Thompson, Perera et al. 2007). In a prospective study examining over 8000 patients referred for investigation, change in bowel habit was the most significant symptom with a positive predictive value for colorectal cancer of 9%, however when combined with rectal bleeding and the absence of perianal symptoms this increased to 20%. When combined with age, this symptom combination achieve a positive predictive value of cancer in the over 80s of over 30% (Figure 1.5) (Thompson, Perera et al. 2007).

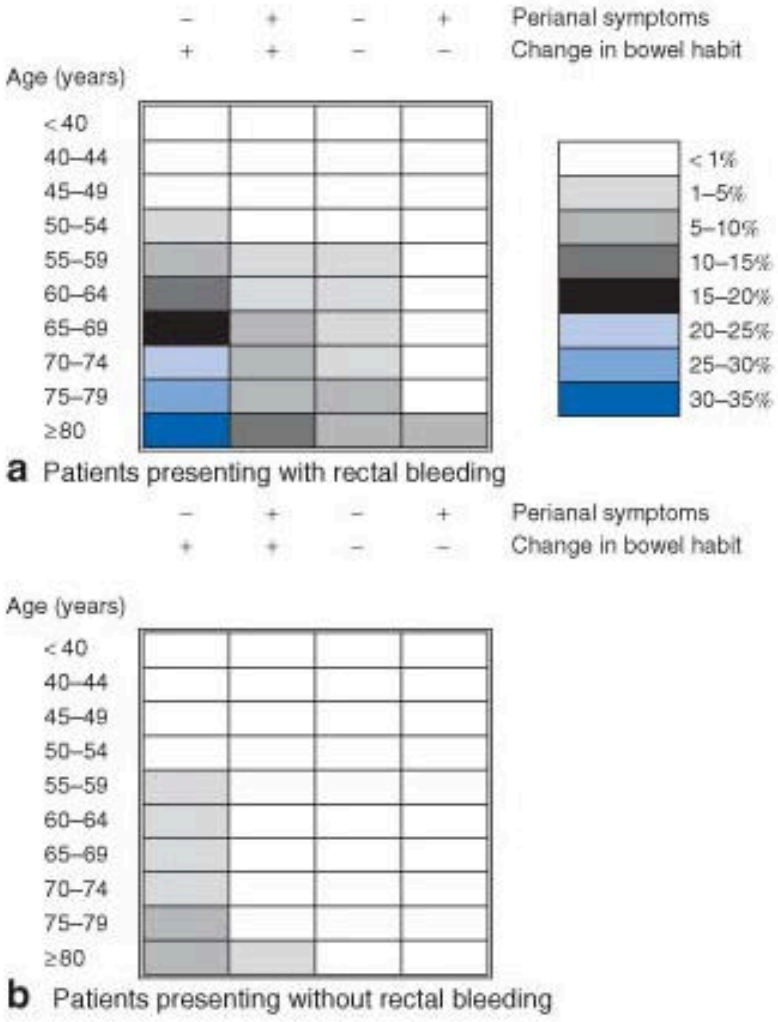


Figure 1.5: The value of symptom combination and age in predicting colorectal cancer risk

(Reproduced from Thompson et al. 2007)

1.1.4.2 Diagnostic investigations

Colonoscopy is currently viewed as the gold standard investigation for patients at risk of colorectal cancer and allows tissue biopsies of identified lesions. Other diagnostic options include CT colonography which has been shown to have good sensitivity for lesions greater than 1 cm. Double barium contrast enema has now been superseded by CT colonography and is rarely used in the UK. A more detailed exploration the sensitivity, specificity and risks of diagnostic investigations is covered in Section 1.2 exploring the accuracy of these tests within a screening setting.

1.1.4.3 Pre-operative staging investigations

Following a tissue diagnosis of invasive cancer, pre-operative staging is required to assess for the presence of metastatic disease, and particularly in the case of rectal cancer, for primary location and local spread. Pre-operatively, computed tomography (CT) of the chest, abdomen and pelvis is routinely used. In the case of rectal tumours, which are defined as being a lesion that is within 15cm of the dentate line when examined by rigid sigmoidoscopy and the patient in the left lateral position, a magnetic resonance imaging scan (MRI) of the pelvis is included to assess for local invasion of the tumour and nodal involvement. Additional imaging includes ultrasound scanning (USS) and MRI to better delineate indeterminate liver lesions identified at CT. Endoanal USS may also have a complimentary role to MRI in examining local invasion and nodal involvement in rectal cancer (NICE 2004; SIGN 2011).

Positron Emission Tomography (PET) can be of use in patients prior to undergoing major resections (i.e. hepatic or lung metastases) to ensure no occult metastatic disease is present, and also in characterising some indeterminate lesions identified on CT. It utilises Fluoro-deoxy-glucose (FDG), which is a positron emission radiotracer that is a marker for uptake of glucose by cells. Therefore, in highly metabolically active tumour cells FDG activity is

usually high and by superimposing PET onto CT scans FDG activity across the body can be monitored. This can also be used in cases where a raised carcinoembryonic antigen (CEA) has been identified with no evidence of colorectal cancer on standard imaging modalities (NICE 2004; SIGN 2011).

1.1.5 Management

1.1.5.1 Surgical intervention

1.1.5.1.1 Surgical resection

The mainstay of management is surgical resection of the affected segment of bowel along with its lymphatic drainage with high ligation of vascular pedicles. If surgical excision is possible, this offers the best chance of good long-term prognosis. Oncological resection is determined by location and blood supply, as is the decision to restore gut continuity with an anastomosis or to exteriorise a stoma.

In the case of rectal cancers the decision has to be made regarding preservation of the anal sphincter complex. This depends on the distance of the cancer from the anal verge. If it is deemed too low to safely preserve the complex, achieve distal margin clearance and provide good rectal function then abdomino-perineal resection (APR) is performed with complete excision of the anus and permanent end colostomy. Recently, more radical APR excisions have involved excision of the levator muscles, so called ‘cylindrical’ or extra-levator APR. Whether or not the sphincter complex is excised, any rectal resection below the peritoneal reflection should involve total mesorectal excision (TME) by preserving the mesorectal fat plane intact as an envelope around the rectum which has been shown to reduce local recurrence rates (Heald and Lockhart-Mummery 1972; Heald and Ryall 1986).

The more distal the anastomosis in the large bowel the higher the risk of anastomostic dehiscence and hence in the case of a low anterior resection a defunctioning loop ileostomy is commonly performed. Stomas are designed to reduce the consequences rather than lessen the prevalence of anastomotic leaks. Risk factors associated with higher rates of anastomotic leak include neoadjuvant radiotherapy, comorbidity, male sex and prolonged

surgery and hence stomas should be considered in such situations (Matthiessen, Hallbook et al. 2004).

1.1.5.1.2 Polyp cancers

Polyp cancers, where the invasive carcinoma is confined to a polypoidal lesion protruding into the lumen of the bowel of where endoscopic resection is primarily attempted, present a surgical dilemma. It is unclear whether such patients can be managed with local resection only or whether a formal oncological resection is required. Such a formal resection would serve to both clear the patient of residual tumour and also to accurately stage the patient through pathological assessment of the lymph nodes harvested. However, there is associated morbidity with a formal resection when compared to endoscopic management alone and hence if this could be avoided it would be of benefit to the patient. Also, a substantial proportion of patients undergoing resection have no residual disease identified (Christie 1984). It could be argued that such patients have undergone an unnecessary operation.

Several criteria have been used to help guide who requires formal resection and have been summarised by SIGN (SIGN 2011). SIGN suggest formal resection should be considered in sessile polyps or in peduculated polyps with invasive carcinoma $\leq$1mm from the resected edge, those with poor differentiation and those with lymphovascular invasion present. Additional staging systems have been proposed, for example the Haggitt criteria. This grades the degree of invasion in pedunculated polyps based on the level of the stalk involved. With those in whom the invasion is confined to the head and neck (levels 1, 2 & 3) having less likelihood of lymphatic involvement compared to those in whom it invades beyond the level of the stalk (Level 4) (Haggitt, Glotzbach et al. 1985).

The Kikuchi criteria can be used for sessile polyps to estimate the risk of lymphatic involvement and splits the submucosa into 3 layers with Sm1 and Sm2 lesions (the inner

2/3 of the submucosa) having a below 10% risk and those with Sm3 having a near 25% risk of involvement of the lymph nodes (Kikuchi, Takano et al. 1995). However, the type of endoscopic resection undertaken limits both of these staging systems. For example, piecemeal excision renders the sample difficult to process and orientate, and, with the Kikuchi criteria, the full thickness submucosa must be present along with some muscularis propria. Such an excision with this depth of resection is not routinely performed endoscopically, however in some situations endoscopic submucosal resection (ESR) can be performed.

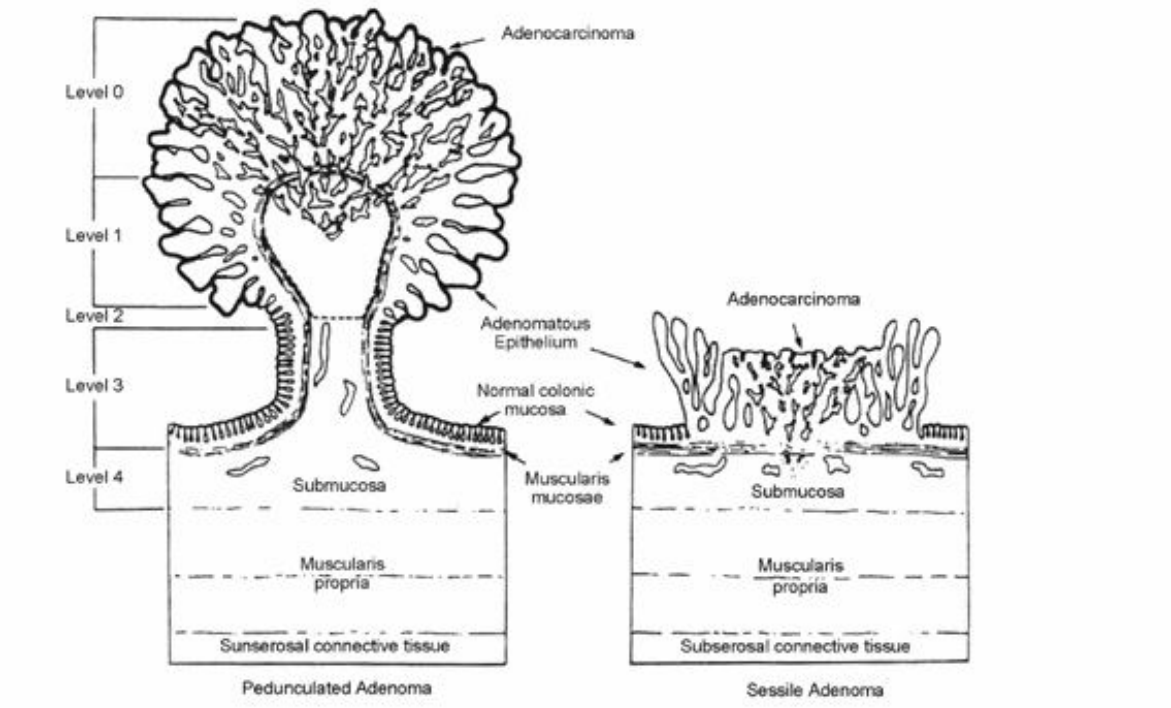


Figure 1.6: Anatomic landmarks of pedunculated and sessile malignant polyps

(Reproduced from Haggitt, Glotzbach et al. 1985)

1.1.5.2 Pathological processing

Following formal surgical resection, specimens should be processed either as fresh or formalin-fixed samples and reported as per The Royal College of Pathologist Guidelines (Williams 2007). This clearly details the macroscopic and microscopic details required for appropriate prognostic stratification. These core-dataset items are summarised in table 1.5. Of note, particular care with the reporting of rectal tumours should be taken and includes a grade of plane of surgical excision such as mesorectal or intramesorectal referring to TME resection. In order to promote high standards of pathological processing, audit standards of a median number of 12 lymph nodes and a venous invasion rate of 30% have been recommended. To achieve improved detection of venous invasion the use of special stains to identify endothelial structures such as elastic stains have been recommended (Roxburgh and Foulis 2011).

Table 1.2: Core-dataset items in pathological reporting of colorectal cancer resections

Macroscopic	• Nature of specimen and type of operation
	• Site of tumour
	• Maximum tumour diameter
	• Distance to longitudinal resection margin
	• Tumour perforation
	• Relationship to peritoneal reflection[a]
	• Grade of plane of surgical excision[a]
	• Distance of tumour from dentate line[b]
Microscopic	• Histological tumour type
	• Histological differentiation
	• Maximum extent of local spread (pT stage)
	• Grade of tumour regression following neoadjuvant therapy
	• Resection margin status (longitudinal and circumferential)
	• Lymph node status; number present/examined, highest node status. (pN stage)
	• Venous invasion (extramural / intramural)
	• Histologically confirmed distant metastases (pM stage)
	• Separate abnormalities (i.e. additional polyps)

[a]rectal tumour only, [b]APR only

1.1.5.3 Neoadjuvant therapy

There is a role for neoadjuvant external beam radiotherapy in some patients with rectal cancers in order to downstage the tumour and improve outcomes. This can have the added advantage of allowing for sphincter preservation. It is currently indicated in rectal tumours with T3/T4 disease, nodal involvement, or threatened or involved circumferential margins suspected on pre-operative imaging (Engstrom, Arnoletti et al. 2009).

Irradiation involves firing high energy electrons from a linear accelerator at a target that causes release of photons. These photons are then directed at the patient to a localised area. This causes an effect on the tumour in three ways: physical, chemical and biological. Physically high speed radiation leads to DNA ionisation and damage. Chemically these damaged atoms interact causing chemical bonds to breakdown and free radicals to form, and biologically these free radicals damage the tumour cell DNA which can lead to cell death. The use of a chemotherapy agent such as capcitabine or 5-fluorouracil (5-FU) has been shown to improve the efficacy of radiotherapy and is commonly used in conjunction (NICE 2004)

There is ongoing debate as to the optimal method of delivering neoadjuvant treatment with short course (larger fractions delivered over a short time frame) and long course (smaller fractions over a longer timeframe) options available (Sign.

1.1.6 Post-operative prognostic stratification

There are a variety of features of both the tumour and the patient, the so-called 'host', that identify patients who are at a higher risk of both local and systemic recurrence. Such features are key, not only to better inform patients, but also to allow risk stratification and hence identification of those who may benefit the most from adjuvant therapy or more intensive follow-up.

1.1.6.1 Tumour factors

1.1.6.1.1 Tumour Stage

Tumour stage remains the main determinant of outcome following both a diagnosis and a resection for colorectal cancer. This can be expressed through either the tumour, node, metastases (TNM) stage produced by the American Joint Committee on Cancer (AJCC) or the Turnbull modification of the Duke's staging (Dukes and Bussey 1958; Turnbull, Kyle et al. 1967). In the UK, TNM 5th Edition is used for staging, as despite newer versions being produced recently that have altered the definition of lymph node involvement, these have limited evidence of clinical reliability (Compton, Fielding et al. 2000). Table 1.6 summarises the staging of colorectal cancer. This can be expressed as clinical (cTNM) or a pathological (pTNM) stage dependent on whether a resection has taken place or not. The prefix of 'y' is used in cases where neoadjuvant therapy has been given (i.e. ypT1ypN0ypM0). In those with residual tumour following neoadjuvant therapy, current figures from the UK estimate 5-year cancer specific survival at 95%, 80%, 66% and 7% with TNM Stage I, II, III and IV disease respectively (Cancer Research UK).

With particular regard to lymph node status there is evidence that the ratio of positive to negative lymph nodes (LNR) may be superior to the actual number of nodes involved in predicting outcome (Rosenberg, Friederichs et al. 2008; Ceelen, Van Nieuwenhove et al.

2010; Rosenberg, Engel et al. 2010). This includes a systematic review including 16 studies and over 30 000 patients (Ceelen, Van Nieuwenhove et al. 2010).

Table 1.3: Staging of colorectal cancer

Dukes Stage	TNM Stage	T-stage	N-stage	M-stage
A	I	T1: Tumour invades submucosa	N0	M0
		T2: Tumour invades muscularis propria		
B	II	T3: Tumour invades through muscularis propria into subserosal or into non-peritonealised pericolic or perirectal tissues	N0	M0
		T4: Tumour directly invades other organs or structures +/- perforates visceral peritoneum		
C1	III	T1-4	N1: 1-3 lymph nodes involved (highest lymph node spared)	M0
			N2: 4+ lymph nodes involved (highest lymph node spared)	
C2		T3-4	N1/2: highest lymph node involved	
D	IV	T1-4	N0-2	M1: distant metastatic disease present

1.1.6.1.2 Additional tumour factors

There is evidence that a variety of additional features of the tumour are related to poor prognosis, and so should be included in the pathological reporting of resected specimens (Compton, Fenoglio-Preiser et al. 2000). Venous invasion, perineural invasion, resection margin status and degree of tumour differentiation have been used to identify high risk node negative tumours (Compton, Fielding et al. 2000). Tumour differentiation has been shown to be associated not only with T stage but also with the presence of lymph node involvement within that stage. For example, Derwinger et al. found that within T2 cancers, low grade tumours had a 17% risk of node involvement versus a 44% risk for those with a high grade tumour (Derwinger, Kodeda et al. 2010).

Peterson et al. established a pathological scoring system for use in Dukes B colonic cancers to stratify risks of loco-regional recurrence. Scores are assigned based on the presence or absence of 4 variables. Peterson Prognostic Index (PI) is 1 if there is peritoneal involvement, plus 1 if extramural or submucosal venous spread is present, plus 1 if the margin is involved or inflamed and plus 2 if tumour perforation is present. A score of 1 or less equated with an 86% 5 year survival compared with a 50% survival in those with a score greater or equal to 2 (Petersen, Baxter et al. 2002).

With regards the components of the PI, more recently the presence of venous invasion has been emphasised as being of particular prognostic importance (Roxburgh, McMillan et al. 2010). The ability to detect venous invasion is improved through the use of elastic staining and such staining improves its role as a prognostic factor (Roxburgh and Foulis 2011).

The presence of tumour necrosis has also been shown to be important in predicting outcome (Pollheimer, Kornprat et al. 2010). Tumour necrosis is thought to develop from tumour ischaemia due to rapid cell growth. It has been shown not only to correlate with more advanced tumour stage, the presence of vascular invasion and the presence of poor

differentiation, but also to be a predictor of poorer cancer-specific survival (Pollheimer, Kornprat et al. 2010; Richards, Roxburgh et al. 2012).

1.1.6.1.3 Tumour genetics

Colorectal cancer can arise from a variety of different genetic alterations and in addition to being associated with the site of tumour these can impact on outcome. Patients whose tumours have high levels of MSI have consistently been shown to have better outcomes compared to those that do not (Soreide, Janssen et al. 2006). There are inconsistencies in determining the prognostic importance of CpG island methylator phenotype (CIMP) positive colorectal cancers particularly in view of the influence of other factors such as MSI (Ogino, Nosho et al. 2009). Work is ongoing to better delineate the link between genetic phenotype and outcome.

1.1.6.2 Host factors

1.1.6.2.1 Patient demographics

Clearly, patient characteristics will impact on outcome following a diagnosis of colorectal cancer. In a large population study from Scotland older patients and those who were more socioeconomically deprived have been shown to have both higher post-operative mortality rates and also poorer 5-year relative survival rates compared to those that are younger and less deprived (Hole and McArdle 2002). These associations appear to be significant independent of comorbidity, stage and emergency presentation that themselves are associated with a poorer outcome. There is also some evidence that males may have a worse outcome (McArdle, McMillan et al. 2003).

1.1.6.2.2 Anaemia

The presence of pre-operative anaemia in patients with colorectal cancer is relatively common and has been shown to be present in 40% of patients with early stage disease and

up to 80% of patients with advanced disease (Knight, Wade et al. 2004). The cause for anaemia is multifactorial and cannot purely be explained by enteric blood loss due to tumour bulk (Dunne, Gannon et al. 2002). There is evidence that it may be related to both nutritional status and the presence of an elevated systemic inflammatory response. In particular, it has a link with the up regulation of pro-inflammatory cytokines in a situation similar to the anaemia of chronic disease (Spivak 2005).

The presence of anaemia has been associated with a worse outcome (Dunne, Malone et al. 2002; Leichtle, Mouawad et al. 2011) as well as identifying those who will have a poorer response to chemotherapy (Tampellini, Saini et al. 2006). Furthermore, there is some evidence that transfusions have been linked to adverse effects on the immune system (Dunne, Lee et al. 2008).

1.1.6.2.3 The systemic inflammatory response

There is increasing evidence that an elevated host systemic inflammatory response is an independent marker of poor outcome in patients with colorectal cancer. This has been quantified by the GPS (Glasgow Prognostic Score) subsequently modified to the mGPS which is a score based on elevated circulating concentrations of C-reactive protein (CRP) and hypoalbuminaemia (McMillan, Crozier et al. 2007; Proctor, Morrison et al. 2011). In brief, an mGPS score of 0 is given when CRP is $\leq$10mg/l; a score of 1 when CRP > 10mg/l and albumin $\geq$35g/l; and a score of 2 when CRP>10mg/l and albumin <35g/l.

Whilst the mGPS has been shown to be related to T-stage, patients with a high mGPS have been shown to have poorer cancer specific survival independent of T-stage (Crozier, McKee et al. 2007) and to have a poorer outcome despite chemotherapy (Crozier, McKee et al. 2006; Ishizuka, Nagata et al. 2007; Ishizuka, Nagata et al. 2009). Moreover, combining the mGPS with an index examining tumour factors, such as the Petersen Index,

can further stratify those patients with node negative colorectal cancer (Roxburgh, Crozier et al. 2009).

1.1.6.2.4 The local Inflammatory response

With regard to the local inflammatory response, there is evidence that the presence of a high grade of local inflammatory infiltrate at the invasive margin is indicative of a better prognostic outcome. There is evidence that both that the adaptive and innate anti-tumour response play key roles in determining cancer progression (Roxburgh and McMillan 2012). Klintrup et al, have simplified the assessment of the inflammatory reaction by looking at the intensity of inflammatory cell reaction by all leucocytes at this margin on routine haematoxylin and eosin staining. Scores were based on the appearances of tumour invasion at the deepest area. A score of 0 to 4 was given for the degree of inflammation at the inflammatory margin. These scores were then subsequently classified as low grade (scores 0 and 1) or high grade (scores 2 and 3). They reported that 5-year survival in TNM Stage I-II cancers was 88% with high grade, compared to 47% with low grade (Klintrup, Makinen et al. 2005).

Clearly interactions between host and tumour characteristics exist and this has important implications for our understanding of the pathogenesis and natural history of early disease. For example, it has recently been shown that the presence of tumour necrosis is closely related to both a poorer local and a more pronounced systemic inflammatory response, themselves all independently identified as predictors of poorer outcome. It has been suggested that necrosis itself may act as a trigger for the systemic inflammatory response (Richards, Roxburgh et al. 2012).

1.1.7 Adjuvant therapy

Following a potentially curative resection for colorectal cancer, adjuvant chemotherapy should be considered in selected patients. This is based on the rationale that occult metastatic disease at the time of operation is responsible for any subsequent recurrence. There are associated side effects with chemotherapy and therefore any adjuvant therapy should involve a considered discussion between patients and health professionals regarding the balance of risks and benefits.

Current guidelines suggest it should be considered in all patients with Stage III disease and in selected patients with Stage II (SIGN 2011). Such high risk Stage II features have been discussed above and include T4 disease, poor differentiation, tumour perforation, inadequately sampled lymph nodes and the presence of extramural vascular invasion (Benson, Schrag et al. 2004).

Commonly combination chemotherapy using cytotoxic drugs is given within 8 weeks of surgery provided the patient has suitably recovered. Cytotoxic drugs act relatively indiscriminately through a variety of mechanisms such as DNA damage impairing cell mitosis, inhibiting the cell cycle and inducing apoptosis. Such drugs include 5-fuorouracil (5-FU), an antimetabolite drug that primarily has its effect through irreversible inhibition of the enzyme thymidylate sythensase which is required for DNA replication (Longley, Harkin et al. 2003) which can be taken in oral form as Capecitabine. Other drugs such as Oxaloplatin, which is a platinum based chemotherapy agent that also acts through inhibition of DNA synthesis, can also be used. Common side effects with oxaloplatin include a severe peripheral neuropathy that can persist for years after treatment. Newer targeted monoclonal antibody therapies such as Cetuximab, an antibody against epidermal growth factor receptor, are now being used either for down staging of liver metastases or in advanced disease (Karapetis, Khambata-Ford et al. 2008). These treatments offer a

promising alternative to cytotoxic agents for some patients with improved side effect profiles and work is ongoing regarding their role in the adjuvant setting.

1.1.8 Follow-up

There is on going debate regarding appropriate follow-up of patients following potentially curative surgery for colorectal cancer. Follow-up programmes are aimed at early detection of recurrent local or metastatic disease with the intention that earlier detection and treatment will result in improved survival. Furthermore, patients are followed up as they are at an increased risk of developing adenomas or a metachronous primary in the remaining large bowel (Heald and Lockhart-Mummery 1972). Additional benefits also include psychological support for patients and the ability of follow-up to aid with audit purposes.

Options for follow-up include clinical assessment, cross-sectional imaging (routinely with CT scanning) and blood based tests such as carcinoembryonic antigen (CEA). Debate exists over the timing and use of such interventions. Current NICE guidelines recommend 6 monthly CEA tests for 3 years after treatment, at least two CT scans of the chest, abdomen and pelvis within 3 years of treatment, and a surveillance colonoscopy at 1 year post treatment (NICE 2004). Guidelines from the Scottish equivalent, SIGN, are less stringent and state that while CEA and CT are useful in detecting recurrent disease, the exact timing is not clear. In addition, they recommend that unless there is a clear indication then there is no requirement for routine colonoscopy until 5 years post treatment and thereafter every 5 years dependent on patient co-morbidity (SIGN 2011).

The reason for such debate is that there is limited high quality evidence that routine follow-up has an impact on survival. Two systematic reviews have examined this and found difficulty with heterogeneity of studies and a lack of information on potential harms and costs associated with follow-up regimes. Overall, both reviews did conclude that intensive follow-up was associated with a moderate improvement in overall survival when compared

to minimal follow-up, but were not able to identify specific factors that were required (Renehan, Egger et al. 2002; Jeffery, Hickey et al. 2007).

1.2 Screening for colorectal cancer

1.2.1 Overview of screening

In order to improve outcome from colorectal cancer, bowel screening programmes have been introduced across the UK in a staged manner over the past 10 years, with the first complete round of the current UK bowel screening programmes being completed in December 2011. There are several key elements underlying population screening (Wilson and Jungner 1968): it must be targeted at an important health issue; the screening procedure should be simple, safe, precise and validated; early stage treatment should be more beneficial than late stage treatment; there should be evidence that screening reduces mortality/morbidity; the benefits should outweigh the harm; the process should be economically viable; the programme should be audited against set standards; and screening participants should be fully informed of the implications of participation. Colorectal cancer is considered to be a good target for screening because it incorporates most of these key elements (Bretthauer 2011).

In addition to this, colorectal cancer also has the apparent advantage of developing from a precursor lesion with what is considered to be a relatively long average interval from the precursor to development of invasive disease. Around 90% of colorectal cancers are adenocarcinomas and are thought to develop from dysplastic polyps, with around 8% of polyps greater than 10mm developing into cancer at 10 years (Stryker, Wolff et al. 1987). It is considered that targeting these adenomas with endoscopic resection should prevent them developing into tumours. As the majority of polyps are symptomless, then a screening tool to identify them should potentially lead to a reduction in colorectal cancer incidence and ultimately improve outcomes. Patients with polyps can be followed up as they are at higher risk of further polyp development and subsequently at a higher risk of developing colorectal cancer (Cairns, Scholefield et al. 2010).

There are currently 2 other population screening programmes for cancer in the UK; breast and cervical.

The Scottish Breast Screening Programme was developed in 1988 and invites all females aged 50 to 70 years for 3 yearly mammograms. It is designed to detect early stage breast cancer and hence reduce cancer specific mortality. Between 2009 and 2010, uptake across Scotland was noted at 75% with recall rates for abnormal mammograms between 10%, for those on their first round of screening, to 4% for those on subsequent screening rounds. In total, looking at figures from 2007 to 2010, there were 6 invasive cancers detected per 1000 woman screened (Scottish Government 2011a).

In Scotland, the cervical screening programme has also been running since 1988 and is available to all women aged 20 to 60 years with 3 yearly screening invites. The procedure involves a smear test assessing for dysplastic cells at the cervix. Rather than being aimed at detecting early disease and reducing cancer-specific mortality, it is designed to reduce the incidence of cervical cancer through removal of precancerous cells. Between 2007 and 2010, uptake of the test across Scotland was 74% with 2.2% of tests having mild dyskaryosis and 1.2% of tests having moderate to severe dyskaryosis that required a further test. Since it's inception the incidence of cervical cancer has fallen by approximately 49% across Scotland (Scottish Government 2011b).

While it is interesting to consider these programmes as a means of comparison for the current bowel screening programmes in terms of uptake and recall rates, it is important to remember that the disease processes they are designed against are different. For example, the overall 5-year unadjusted cancer specific mortality is 15% with breast cancer and 33% with cervical cancer compared to 45% with colorectal cancer (Cancer Research UK).

1.2.2 Options for screening for colorectal cancer

1.2.2.1 Colonoscopy

Colonoscopy is currently viewed as the gold standard for imaging the large bowel and identifying colorectal cancer, with superior sensitivity and specificity to other methods. A flexible fibreoptic tube is passed per rectum to the caecum allowing for direct luminal visualisation and biopsy of any lesions identified. It is, however, an invasive test with a complication rate of colonic perforation of approximately 0.05% (Lorenzo-Zuniga, Moreno de Vega et al. 2010). There are also resource and cost issues in instigating this as an initial screening tool. Also, the public acceptance of undergoing endoscopic evaluation of the large bowel is at present thought to be limited. For example, when flexible sigmoidsocopy was compared to stool sampling tests in a screened population compliance rates with non-invasive testing were almost double that of the endoscopic group (Hol, van Leerdam et al. 2010).

While it is accepted as the standard for large bowel imaging it is important to note that there have been no randomised trials published examining the effect of population colonoscopy screening and outcome. There is, however, currently a large randomised control trial underway, comparing colonoscopy with CT colonograpy as a primary population screening tool for colorectal cancer (de Wijkerslooth 2010). It will require long term follow to assess its efficacy in reducing cancer specific mortality.

1.2.2.2 Flexible sigmoidoscopy

As the majority of tumours occur distal to splenic flexure (Cancer Research UK), flexible sigmoidoscopy has been proposed as a screening tool. Several randomised controlled trails have been conducted examining this. The UK flexible sigmoidoscopy screening trial (Atkin, Edwards et al. 2010) was the largest of these and enrolled 170 000 people aged 55-

64. Participants were assigned at random to either receive a once off screening flexible sigmoidoscopy or no screening at all. There was a 71% uptake of the test and over 11 years those that attended the test had a reduced incidence of colorectal cancer of 23% and reduced cancer specific mortality of 33%. The trial however only enrolled those that had previously expressed an interest in participating and was therefore not a population based trial. There remains doubt as to the compliance that can be achieved with a population screening flexible sigmoidoscopy programme and to whether current endoscopy resources would be able to provide it. However, it has now been introduced as an adjunct to the screening programme in England and pilot studies are underway in Scotland to do similar. The use of flexible sigmoidoscopy as a screening tool has other inherent issues such as the very definition of what a 'complete' flexible sigmoidoscopy is and these are discussed in more detail in Chapter 4.

1.2.2.3 CT colonography

CT colonography allows for non-interventional assessment of the colon and rectum. It requires limited bowel preparation prior to the procedure and then the individual to pass through a CT scanner for 3D imaging while air is insufflated per rectum to distend the large bowel. It has been shown to have a comparable sensitivity and specificity with colonoscopy for colorectal cancer and for polyps greater than 10mm (Halligan, Altman et al. 2005; Pickhardt, Hassan et al. 2011). No randomised trials have been published examining cancer specific mortality with regards to CT colonography screening, however uptake and individual acceptance of the test has been found to be more favourable than colonoscopy (de Wijkerslooth 2010).

Clearly, the downside is a requirement for subsequent colonoscopy in order to directly visualise and remove any lesions identified, and this two stage process has considerable resource and cost implications to healthcare providers and patients. Also, there is a not-

insignificant radiation dose associated with the procedure, averaged at 5.7 mSv equivalent to approximately 57 plain chest X-rays (Liedenbaum, Venema et al. 2008). In addition there have been reports of colonic perforations (Bassett, Liotta et al. 2008). One further point on CT colonography is that it detects extracolonic intra-abdominal abnormalities. The incidence of significant findings requiring either further investigation or operation is thought to be around 11% (Veerappan, Ally et al. 2010). Such incidental findings can be viewed as either an advantage of screening or as a drawback, depending on how individuals are consented prior to the procedure. For example, an abnormal liver area requiring further interval scanning that ultimately turns out to be benign may cause undue anxiety to an individual who had only consented to have screening of their colon.

1.2.2.4 Faecal occult blood tests

The screening tool currently in use in the UK is the stool based faecal occult blood test (FOBt). Currently in use as a first line test is a guaiac-based test that detects the peroxidase activity of haematin in faeces (gFOBt). In the case of a weakly positive test, a confirmatory Faecal Immunochemical Test (FIT) is used in Scotland, Wales and Northern Ireland. In England, following a weakly positive gFOBt, a second gFOBt is used as a confirmatory test. The FIT specifically targets human haemoglobin and, rather than the binary response that the gFOBt produces, FIT tests have the potential to be quantitative. This allows cut-off thresholds to be determined based on relative sensitivity and specificity of the test. With the use of an optimal threshold, FIT has been shown to have a higher sensitivity for advanced neoplasia and a similar specificity (Hol, Wilschut et al. 2009). The gFOBt has the disadvantage of being positive when certain foods are eaten such as animal food products high in haem content (e.g. raw meat) and raw peroxidase-rich fruits and vegetables (e.g. broccoli and cauliflower)(Caligiore, Macrae et al. 1982). Therefore, gFOBt can have a higher false positive rate than FIT, however this will be dependent on the

threshold of FIT used. There is an option to rehydrate a gFOBt for processing, with rehydration increasing the sensitivity but decreasing the specificity of the test. Tests are not currently rehydrated in the UK. The FOBt based screening programmes are less invasive and have higher compliance rates than endoscopic programmes, however they have a lower sensitivity and specificity (Levin, Lieberman et al. 2008; Hol, van Leerdam et al. 2010).

1.2.2.5 DNA stool tests

There has been some progress in the use of stool tests that have molecular assays for DNA mutations and methylation biomarkers that are associated with colorectal cancer. Initially these tests were very expensive and had limited sensitivity and specificity, overall conferring no great advantage over faecal occult blood screening tests (Imperiale, Ransohoff et al. 2004; Ahlquist, Sargent et al. 2008). However, advances in the processing of samples and the use of more discriminate markers has led to an overall improvement in test characteristics. Several studies are on going assessing the efficacy of such tests and will be publishing results in the near future (Ahlquist 2010).

1.2.2.6 Systemic markers

As discussed previously, it is proposed that cancer-related inflammation is the seventh hallmark of cancer (Hanahan and Weinberg 2000; Colotta, Allavena et al. 2009) and that it is essential in causing activation of oncogenes and inactivation of oncosuppressors. Therefore, it would seem prudent to assume that patients with an elevated systemic inflammatory response have a higher propensity to develop cancer. Therefore, testing serum markers of an elevated systemic inflammatory response may be a useful screening tool. To date, the role of elevated C-reactive protein levels within a bowel screening programme has yet to be examined.

Table 1.4: Comparison of test characteristics of commonly used population screening tests for colorectal cancer
(Adapted from Bretthauer 2011)

	Cancer sensitivity (%)	Advanced adenoma sensitivity (%)	Cancer specificity (%)	Advanced adenoma specificity (%)
gFOBT	11-64	11-41	91-98	n/a
FIT	56-89	27-56	91-97	n/a
Flexible Sigmoidoscopy	60-70	50-81	60-70	50-80
Colonoscopy	95	95	95-99	90-95

1.2.3 Background evidence underpinning the UK bowel screening programmes

Bowel cancer screening was introduced in Scotland in a staged manner from 2007 following the results of three major randomised control trials (Mandel, Bond et al. 1993; Hardcastle, Chamberlain et al. 1996; Kronborg, Fenger et al. 1996) and a Cochrane review (Towler, Irwig et al. 2000) that examined the use of gFOBt as a population screening tool. In these trials, patients testing positive on gFOBt were referred on for assessment with a view to undergoing a colonoscopy.

The Minnesota trial (Mandel, Bond et al. 1993) enrolled 46,551 patients aged 50 to 80 and randomised them to 3 groups (annually screened, biannually screened and a control group). In the annual screened group, uptake was on average 75% and a reduction in cancer specific mortality of 33% was seen after a median of 13 years versus the controls. The biannual group uptake was at 78% while a reduction of mortality in 6% was seen in a similar follow-up. In this study the gFOBt was rehydrated and no dietary restrictions imposed so the overall positivity rate was relatively high at 10%.

The Funen study (Kronborg, Fenger et al. 1996) randomised 61,933 patients between the ages of 45 and 75 into a control group and a group undergoing biannual screening. Uptake was at 67% and after a median of 10 years a reduction of cancer specific mortality of 10% was seen. Tests were not rehydrated and dietary restrictions were imposed giving a 1% positivity rate.

The Nottingham trial (Hardcastle, Chamberlain et al. 1996) identified over 150,000 people aged 45 to 74 over a ten year period and randomised them to undergoing biennial gFOBt or not. 60% uptake was achieved and of these 38% completed all the tests during the time period. After a median of 8 years follow-up, a 15% reduction in cancer specific mortality

in the screening group was found. Tests were not rehydrated and dietary restrictions only imposed in borderline cases with a positivity rate of 2%.

The results of these trials were the subject of a Cochrane review in 2000 (Towler, Irwig et al. 2000). This noted that screening benefits included reduction in colorectal cancer mortality, possible reduction in cancer incidence through detection and removal of colorectal adenomas and potentially, treatment of early colorectal cancers may involve less invasive surgery. However, it noted the harmful effects of screening including the physical complications of colonoscopy, disruption to lifestyle, stress and discomfort of testing and investigations, and the anxiety caused by false positive screening tests. For example, if 10 000 people are invited to screening, and two-thirds choose to take part, 8.5 deaths would be prevented within 10 years, however 2800 patients will have undergone colonoscopy through the programme. Nevertheless, it was felt that the screening benefits were likely to outweigh harm for populations at increased risk of colorectal cancer, however more information was required prior to widespread adoption of a screening policy (Towler, Irwig et al. 2000).

The evidence prompted the introduction of a pilot bowel screening programme in 2000 in 2 health authorities in England and 3 health boards in Scotland involving a total of 478 250 people aged 50-69. Results were similar to the Funen and Nottingham studies with uptake at 57%. The positive predictive values of finding a cancer at colonoscopy following a positive gFOBt screening test in the Scottish population was 12% and of a cancer or adenoma of 47% (UK Colorectal Cancer Screening Pilot Group 2004).

A further Cochrane review published in 2007 and subsequently updated in 2010 (Hewitson, Glasziou et al. 2007) performed a meta-analysis of the risks and benefits of screening with regards the follow up data from the 3 initial trials (Minnesota, Nottingham, Funen) and included a fourth trial published from Gothenburg in 2008 (Lindholm,

Brevinge et al. 2008). Overall, based on biennial screening, a reduction of colorectal cancer mortality of 15% was seen and in those who took up testing this increased to a 25% reduction. Median follow up in this updated review was 18 years for Minnesota, 17 years for Funen, 15 years for Gothenburg and 11 years for Nottingham. There was no reduction in all-cause mortality as cancer-related mortality is associated with only a small proportion of deaths in early stage disease.

Table 1.5: Summary of gFOBt trials

Trial	N	Intervention	Uptake	+gFOBt rate	%+gFOBt undergoing full investigation	No. of CRC N (%+gFOBt)	No. of Adenoma ≥10mm n(%+gFOBt)	Tumour Stage[a] N (% total screen detected)					Mean/ Median F/U (Years)	Reduction CRC spec mortality
								I	II	III	IV	n/a		
Funen, 1996	30,967 screened 30,966 control	45-75 yrs -Biennial FOBt Dietary restrictions, non rehydrated	67%	1%	89%	37 (17%)	68 (32%)	48 (40%)	43 (36%)	19 (11%)	8 (7%)	2 (2%)	10	16%
Nottingham, 1996	76, 466 screened 76,384 control	- 45-74 yrs - Biennial FOBt - Dietary restriction only in borderline cases, non re-hydrated	53%	2%	-	83 (10%)	273 (33%)	42 (51%)	17 (20%)	20 (24%)	4 (5%)	0	8	15%
Minnesota, 1993	15,570 screenA 15,587 screenB 15,394 control	50-80 yrs Annual (screenA) Biennial (screenB) FOBt No dietary restriction, re-hydrated kits	75% (A)[c] 78% (B)[c]	9.8%	83%~ 84%~	(1-5%)[b] (1-6%)[b]	(6-8%)[b] (7-10%)[b]	107 (30%) 98 (27%)	101 (29%) 95 (26%)	80 (23%) 100 (27%)	33 (9%) 41 (11%)	33 (9%) 34 (9%)	13	6% 33%
Gothenburg, 2008	34, 144 screened 34, 164 control	60-64 yrs Either 2 or 3 rounds of FOBt Dietary restrictions, re-hydrated kits	63%	3.8%	87%	47 (6%)	114 (14%)	44 (42%)	29 (28%)	24 (23%)	7 (7%)	0	16	16%

1st Round results and Follow-up mortality data unless otherwise specified

[a] Nottingham: figures represent tumours picked up with a +ve FOBt and subsequent colonoscopy 1st round only. Funen & Gothenburg: figures represent total amount of tumours diagnosed in screened cohort following a +FOBt and subsequent colonoscopy over during trial and follow-up period. Minnesota: figures represent total amount of tumours diagnosed in screened cohort including those who declined screening over trial and follow-up period.

[b] Based across all screening rounds PPV for cancer/adenoma. Range shown from 1 to 6 positive slides on FOBt

[c] Average across all screening rounds

1.2.4 The current Scottish Bowel Screening Programme pathway

The SBoSP was introduced in a staged manner across Scotland from 2007 onward and is run by each individual healthboard. This began on NHS GG&C in April 2009. All males and females between the age of 50 and 74 and registered with a General Practitioner (GP) are identified via their Community Health Index (CHI) and invited to participate. Each participant is initially sent a pre-notification letter advising them that they would be receiving an invite to participate in the screening programme. This has been shown to increase participation (Libby, Bray et al. 2011). Each participant is then sent a gFOBt kit and asked to provide 2 samples from 3 separate faecal specimens (hema-screen, Immunostics, Ocean, New Jersey, USA, supplied by Alpha Laboratories, Eastleigh, Hampshire, UK). These are deposited on 6 oval windows provided in the kit and then the kit returned to the Scottish Bowel Screening Centre (Kings Cross Hospital, Dundee) for analysis in a pre-marked foil envelope (Figure 1.7). This is a purpose built test screening centre where tests are processed by hand. Tests are not rehydrated on arrival at the analysis centre and no dietary restrictions are imposed on test subjects.

Tests are classified as positive if 5 out of 6 windows are positive, and weakly positive if 1-4 windows are positive. In the case of a weakly positive result or a spoiled gFOBt kit, a further faecal immunochemical test (FIT) kit is sent out (hema-screen SPECIFIC, Immunostics, Ocean, New Jersey, USA, supplied by Alpha Laboratories, Eastleigh, Hampshire, UK) (Fraser, Digby et al. 2012). The cut-off levels for a positive result for the gFOBt and FIT tests are 600μg Hb/g faeces and 10 μg μg Hb/g faeces respectively.

Following an overall positive test result, the local healthboard is contacted and are responsible for arranging further investigation. Individuals are pre-assessed, either face-to-face or following telephone consultation, by a bowel screening endoscopy nurse and then referred on for colonoscopy if this is deemed suitable. The majority of patients in NHS

GG&C are pre-assessed via telephone consultation. If colonoscopy is unsuccessful then further bowel imaging by barium enema or CT pneumocolonography is attempted. In the case of a negative test the patient is re-invited 2 years later at their next screening round. For patients over the age of 74 who are no longer automatically invited, an opt-in system is possible if they so wish. The screening algorithm is summarised in Figure 1.7.

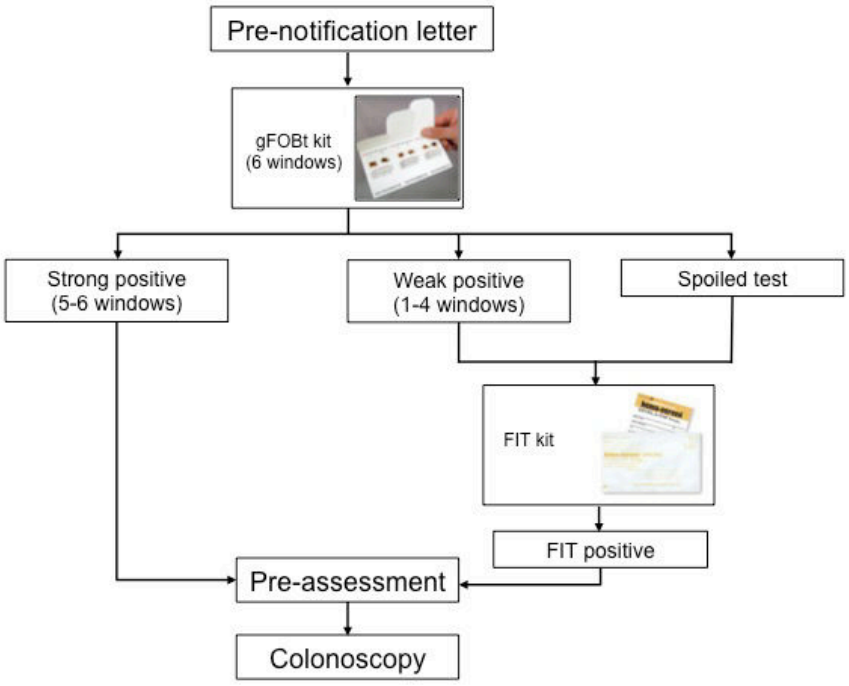


Figure 1.7: Current Scottish Bowel Screening Programme algorithm

Figure 1.8: Scottish Bowel Screening Centre (Kings Hospital, Dundee)

1.2.5 Risks of colorectal cancer screening

1.2.5.1 Complications of endoscopic procedures

The major advantage of stool-based tests is that they are non-invasive. However a proportion of patients will undergo colonoscopy following a positive test and this is a procedure that is not without risk. Notably, there is a risk of perforation and significant haemorrhage. A previous study looking at over 25 000 colonoscopies quoted a perforation rate of 0.05% and a risk of post polypectomy bleeding of 0.15% (Lorenzo-Zuniga, Moreno de Vega et al. 2010). Clearly these risks will alter depending on the pathology found with those undergoing polypectomy at a higher risk of adverse events. Higher rates of adverse outcomes are associated with low-volume endoscopists and the presence of larger polyps (Lorenzo-Zuniga, Moreno de Vega et al. 2010).

1.2.5.2 Psychological impact of screening

In addition to the physical harm that can be caused by an endoscopic procedure there are further psychological impacts on the individual. For example, it has been suggested that the stress of a false positive result can adversely affect an individual. In a recent questionnaire study examining 600 individuals who had responded to a gFOBt screening invitation, it was found that anxiety levels were higher in those who tested positive compared to those who were negative and this persisted to 3 months post-result although had returned to normal by 12 months (Brasso, Ladelund et al. 2010). Interestingly there was no difference in the pattern of anxiety levels between those with true positives and those with false positives indicating that the stress is related to the process of subsequent investigation rather than the disease identified (Brasso, Ladelund et al. 2010).

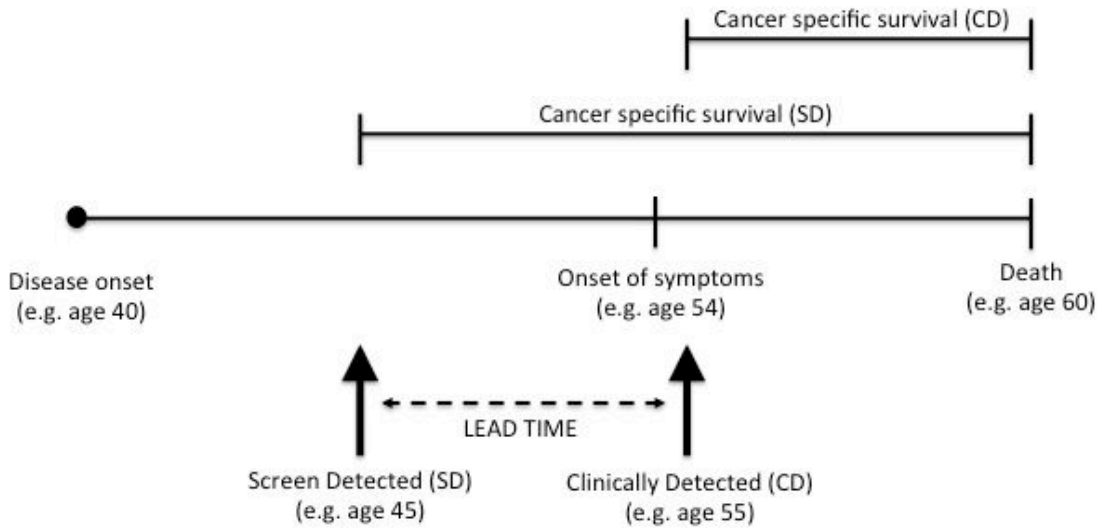
The converse of this is the potential reassuring nature that a negative result can have. In a population-based colonoscopy screening trial (n=225), 30% of patients actually had improved mental health scores post procedure when questioned at 5 weeks with no

difference between those who had polyps and those who had normal colonoscopies found (Taupin, Chambers et al. 2006). There were no cancers found in this relatively small patient cohort. The applicability of this being limited to colonoscopy, which has a much higher sensitivity than FOBt, is important to note. The issue with FOBt is that of false negatives that may falsely reassure an individual that colorectal cancer is not present. A previous study has noted that a negative gFOBt was associated with a delay to presentation in symptomatic patients (Schnell, Aranha et al. 1994).

1.2.5.3 Lead-time and Length-time bias

One of the criticisms of screening and analysis of data from screening programmes is that it can introduce two clear forms of bias (Kay and Witte 1991). The first is lead-time bias, where an earlier diagnosis of cancer in a pre-symptomatic phase artificial elongates an individual's cancer-specific survival without altering that individual's date of death (Figure 1.9a). Secondly there is length time-bias, where the identification of indolent slow growing tumours artificially improves overall cancer-specific survival by detecting those who have a longer pre-clinical phase (Figure1.9b). The extreme form of length-time bias is overdiagnosis, whereby screening detects and eliminates tumours that may not have become apparent within a patients lifetime (Kay and Witte 1991). There is evidence from breast cancer screening that such overdiagnosis occurs, with a higher incidence of cancer being diagnosed in those who are invited to screening when followed up over 10 years (Allgood, Duffy et al. 2011). There is currently no evidence to support this phenomenon in colorectal cancer screening.

(a)



(b)

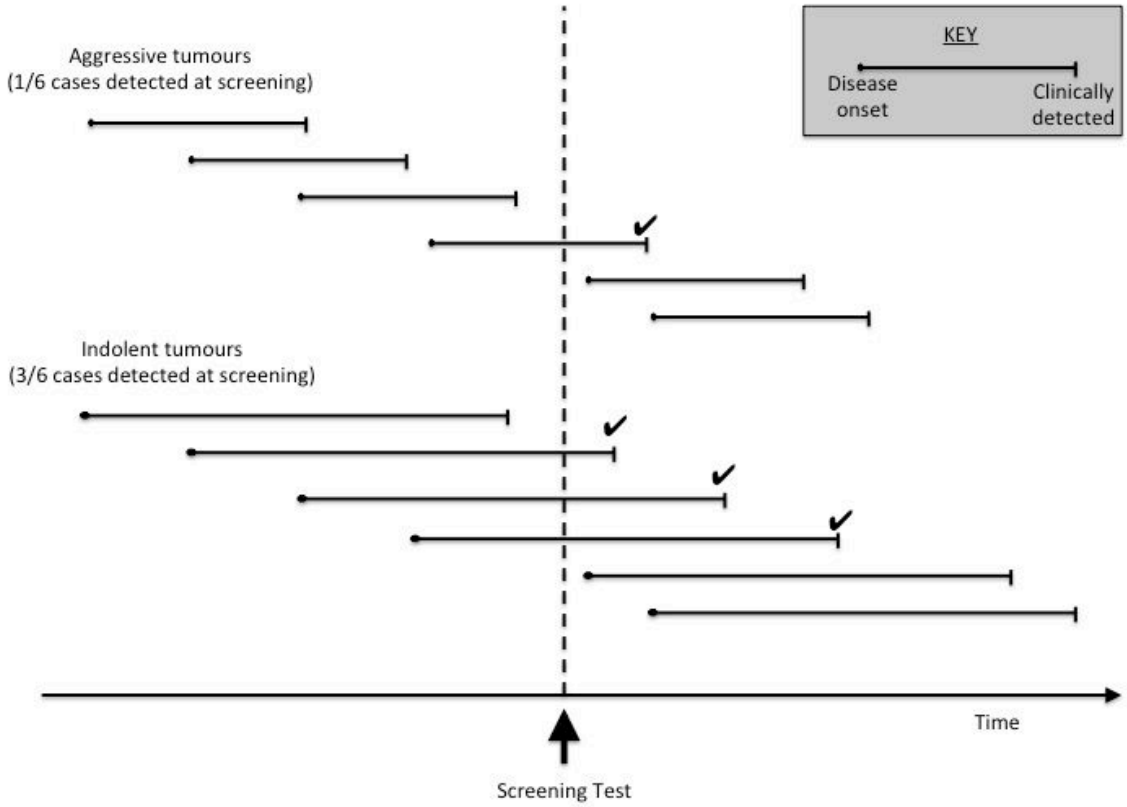


Figure 1.9: Schematic representation of lead-time (a) and length-time (b) bias

(Adapted from American College of Physicians)

1.3 Summary and Aims

1.3.1 Summary

Colorectal cancer is the third most common cause of cancer and the second most common cause of cancer death in the Western World. Outcome is directly related to stage at presentation, with those patients diagnosed at an earlier stage having excellent outcome following surgery and not requiring adjuvant therapy. However, independent of TNM Stage there are additional prognostic factors that have been shown to be of importance in determining outcome. These include features of the tumour, such as poor differentiation and venous invasion, and host-related factors both in terms of demographic profile and an elevated circulating host inflammatory response that are predictive of a worse outcome.

Symptoms related to colorectal cancer can be non-specific and may not become apparent until tumours are at a more advanced stage. Hence a reliance on symptoms to aid with diagnosis of early-stage disease is problematic. There has therefore been an emphasis placed on screening patients either through stool based tests or endoscopic methods. While endoscopic methods have been shown to have improved sensitivity and specificity over stool tests, they are both invasive procedures, with associated risks, and resource intensive. Population screening for colorectal cancer using FOBt has therefore been introduced following three major randomised control trials and a Cochrane review that have show a reduction in cancer-specific mortality through the detection of early stage disease. However, there are concerns with this type of screening relating to uptake and test characteristics, and its impact at a population level has yet to be fully examined or proven. This is particularly important in the West of Scotland which is an area with high levels of socioeconomic deprivation.

While population FOBt screening has been shown to detect early stage disease in those patients who choose to participate, it has been suggested that it may be limited in terms of

its ability to detect certain types of tumour such as more proximal colonic disease. Moreover, there is some evidence from screening programmes for other cancers, such as breast cancer, that screen-detected tumours may be different to non screen-detected tumours in terms of their phenotype. This has yet to be studied in detail within a population undergoing FOBt colorectal cancer screening. In addition, no study to date has explored important additional tumour and host prognostic factors, outside of TNM Stage, as discussed above, in relation to screening.

Screening leads to the detection of early stage disease where the majority of patients will have a good outcome. However, within this some will develop recurrent or metastatic disease and ultimately succumb to their disease. There is a paucity of evidence examining determinants of outcome in TNM Stage I disease as prior to screening this made up a low proportion of patients encountered in clinical practice. It is therefore imperative that prognostic factors previously validated in TNM Stage II disease are assessed in TNM Stage I disease.

Large population databases created through the organisation of screening programmes can be utilised not only to assess screening efficacy, but also to help explore additional factors associated with outcome in colorectal cancer. For, example, utilising screening data can improve our understanding of the development of symptoms and their relationship to disease progression. In addition, current concepts in chemoprevention can be examined by investigating relationships between potentially chemopreventative medications and outcomes at colonoscopy. This is something that has yet to be undertaken in detail and with substantial numbers within a screening programme.

It has previously been reported that the majority of patients undergoing colonoscopy following a positive FOBt do not have colorectal cancer and a large proportion have premalignant adenomatous polyps. Stratification and prediction of outcome in these

patients is difficult and guidelines are currently reliant on characteristics of the adenomas removed. While the host inflammatory response has previously been examined in malignant disease, there is little evidence examining its role in adenomatous polyps. Such an understanding may aid not only with stratification but also with our understanding of the host inflammatory response to pre-malignant disease.

The introduction of screening for colorectal cancer has not only the potential to alter the stage of disease at presentation and long term survival, but also the clinical management of the disease through a more fundamental understanding of the natural history. It is therefore important to examine the impact of colorectal cancer screening on the tumour and host related determinants of outcome.

1.3.2 Aims

The first round of the population-based FOBt colorectal cancer screening in NHS Greater Glasgow & Clyde was used as a backdrop to examine in detail the areas of uncertainty described throughout the course of the introduction. The following studies were therefore carried out:

1. To investigate the changes in mode, site and stage of presentation of colorectal cancer that have accompanied the introduction of the national screening programme

2. To examine the first round of screening in detail with regards to the impact of age, sex and socioeconomic deprivation throughout all stages of the screening process.

3. To examine the impact of altering the current screening algorithm to include flexible sigmoidoscopy following a positive FOBt, rather than colonoscopy, and assess the impact on neoplasia detection rate

4. To examine the relationship between Aspirin, Statins and ACE-inhibitor usage and outcome at colonoscopy following a positive FOBt

5. To examine the relationship between colorectal symptoms and outcome at colonoscopy following a positive FOBt

6. To examine the sensitivity and specificity of the first round of screening and compare and contrast screen-detected and non screen-detected colorectal cancer

7. To examine tumour and host determinants of outcome in TNM Stage I colorectal cancer

8. To examine the interrelationships between tumour and host clinicopathological characteristics in screen-detected T1/2 colorectal cancer

9. To examine the local inflammatory response in screen-detected non-malignant disease and assess it relationship to polyp characteristics

2 COLORECTAL CANCER IN THE WEST OF SCOTLAND: A DECADE OF EXPERIENCE

2.1 Introduction

Several large randomised control trials examining guaiac-based Faecal Occult Blood test (gFOBt) colorectal cancer screening programmes have shown a reduction in cancer specific mortality through the detection of early stage disease (Mandel, Bond et al. 1993; Kronborg, Fenger et al. 1996; Scholefield, Moss et al. 2002). Therefore, national bowel screening programmes have been introduced across the UK over the past ten years. However, it is important to consider screening within the context of the whole population that is being served by the screening programme. For example the current Scottish Bowel Screening Programme (SBoSP) is only targeted to those aged 50 to 74 years, with a few over the age of 74 opting in to further testing. In addition there is limited uptake, sensitivity and specificity of the testing algorithms in use. Therefore, clearly, not all tumours will be screen-detected and it is unclear what the overall impact on the population will be.

Indeed, a previous single centre study from Scotland has suggested that screen-detected tumours may account for just 17% of all tumours diagnosed within a population invited to screening (Roxburgh, McTaggart et al. 2013). Additionally it had been noted that despite screening detecting an increased number of early stage tumours, it may not lead to an overall stage-shift to earlier disease across the population (Roxburgh, McTaggart et al. 2013). However, there are additional benefits that may be gained from screening. For example, it may reduce the rate of emergency presentation (Scholefield, Robinson et al. 1998) which has been noted to be an independent negative prognostic feature in colorectal cancer (McArdle and Hole 2004).

The aim of the present Chapter was to examine the impact that screening has had on the mode, site and stage of presentation of colorectal cancer in the West of Scotland over the

past decade. The aim was to achieve this by using population statistics from the West of Scotland Managed Clinical Network (MCN) to compare cohorts before, during and after the introduction of the SBoSP.

2.2 Materials and methods

The West of Scotland Colorectal Cancer Managed Clinical Network (MCN) covers 4 Health Boards (Ayrshire & Arran, Forth Valley, Greater Glasgow & Clyde and Lanarkshire) comprising 16 different hospitals and covering a population of over 2.4 million, just under half of the population of Scotland (Figure 2.1). It was created in 2000 with the aim of improving outcomes in colorectal cancer. All patients discussed at a local hospital multidisciplinary team (MDT) with a diagnosis of colorectal cancer are included, with clinicopathological data prospectively recorded. Details including age, sex, socioeconomic deprivation category, mode of presentation and tumour site and stage are routinely stored. For the present study, data was extracted for a period from 1st January 2003 to 31st December 2012.

The mode of presentation was defined as emergency if the patient underwent management involving a hospital admission that was unplanned. This included but was not limited to significant per rectal bleeding, colonic obstruction and perforation. Other routes were defined as elective including screen-detected which was introduced as a data-point from 2007 onward.

Tumour site was classified according to anatomical site as per International Classification of Disease version 10 (ICD-10). Lesions up to but not including the splenic flexure were classified as right sided (C18.0 – C18.4), those from splenic flexure up to but not including the retosigmoid junction were defined as left sided (CC18.5 – C18.7) and tumours of the rectosigmoid junction and rectum were classed as rectal (C19 and C20). Tumour stage was defined according to the standard TNM (version 5) classification (Sobin and Fleming 1997) based on histological resection of specimens and, in those who did not under go resection, on pre-operative imaging modalities. Polyp cancers, which underwent endoscopic excision only, were classified as TNM Stage I disease. Intent of procedure was

collated at the time of resection as either curative or palliative by the surgical team responsible for each individual patient.

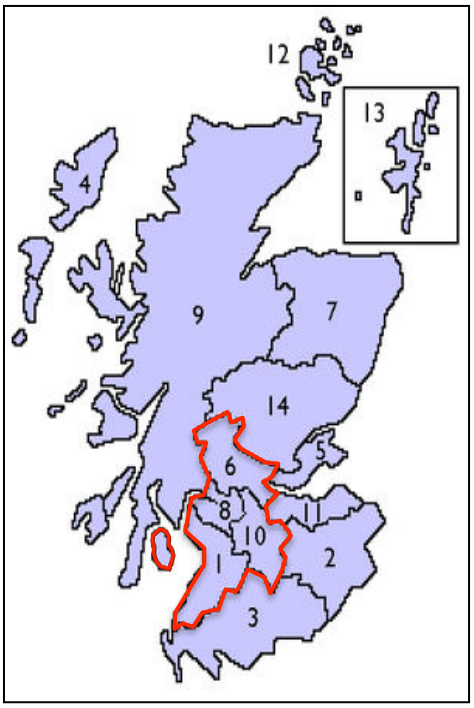
Socioeconomic deprivation status was calculated from the Scottish Index of Multiple Deprivation (SIMD) which is an index of relative deprivation (SIMD 2009). Quintiles of deprivation were used to assign individuals a relative deprivation category based on their postcode at time of diagnosis with the first quintile representing the most deprived and the fifth quintile, the least deprived. The most current version of SIMD was used at the time of data collection (i.e. SIMD 2004 for patients in 2003 to 2005, SIMD 2006 for patients in 2006, 2007 and 2008 etc.)

The SBoSP is a biennial gFOBt/FIT based screening programme for all individuals aged 50-74 years. Details on the current screening algorithm have been covered in Chapter 1. Briefly, all individuals aged 50-74 years are sent a pre-invitation letter and then a gFOBt and referred for colonoscopy if this is returned and is strongly positive ($\geq$5 of 6 windows positive). In the case of a weakly positive gFOBt (1-4 of 6 windows positive) or spoiled or untestable kit a confirmatory Faecal Immunochemical Test (FIT) is sent. Individuals then proceed to colonoscopy, following pre-assessment, by a bowel screening pre-assessment nurse. Screening was introduced across the 4 Health Boards at staged intervals (Figure 2.1), therefore, the data was separated into 5 distinct time frames. 2003-2004 early pre-screening (EPrS), 2005-2006 late pre-screening (LPrS), 2007-2008 early introduction of screening (ES) where the minority of the population were invited, 2009-2010 late introduction of screening (LS), where the majority of the population were invited and 2011 to 2012 post introduction of screening (PoS) where screening had been introduced across all 4 boards. This allowed for assessment not only of the impact of screening but also of the temporal changes in disease presentation and management across the area across the decade.

Permission for the study was granted by the Caldicott guardian for the data and all data was stored and analysed in an anonymised manner

Statistical analyses

Associations between categorical variables were examined using χ^2 tests for linear trend unless otherwise specified. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA)



	NHS Health Board	Population (est. 2009)	Screening Introduction	Screening uptake (%)[a]
1	Ayshire & Arran	372 380	September 2007	55
2	Borders	113 380	November 2009	60
3	Dumfries & Galloway	151 160	December 2008	58
4	Western Isles	27 420	July 2008	57
5	Tayside	404 390	June 2007	59
6	Forth Valley	294 140	December 2007	55
7	Grampian	559 210	June 2007	61
8	Greater Glasgow & Clyde	1 199 830	April 2009	53
9	Highland	318 200	December 2009	61
10	Lanarkshire	569 800	August 2009	48
11	Lothian	816 640	May 2008	54
12	Orkney	20 940	October 2007	63
13	Shetland	22 790	October 2009	64
14	Fife	361 410	June 2007	56

[a]derived from invitations between 1st November 2010 and 31st October 2012 (ISD, 2013)

Figure 2.1: Population of NHS Health Boards across Scotland, area covered by the MCN, date of screening introduction and uptake of test

(Adapted from Information Services Division Scotland)

2.3 Results

From 1st January 2003 to 31st December 2012, there were 14487 incident cases of colorectal cancer. There were 7827 (54%) males, 9912 (69%) were over the age of 65 years and the majority were in the two most deprived quintiles of deprivation (7727 (53%)). Overall, 2163 (15%) patients presented to surgery as an emergency (Table 2.1).

On examining patient demographics over the decade of analysis, there were no changes seen in the age and sex of patients at diagnosis, however there was a weak trend for those in PoS to be more deprived in later years (p=0.057). There was a significant reduction in the proportion of patients presenting to surgery as an emergency over the timeframe from 20% EPrS to 13% PoS (p<0.001) (Table 2.1).

On examining tumour characteristics, there was a reduction in the proportion of rectal cancers diagnosed over the timeframe from 34% EPrS to 31% PoS (p=0.001). Comparing procedure intent, excluding those who did not undergo a procedure, more patients underwent a procedure with a curative intent in later years (76% EPrS vs 84% PoS, p<0.001) (Table 2.1). Overall, 3379 (23%) patients had incomplete TNM staging information and 708 (5%) patients had evidence of distant metastatic disease. These were subsequently excluded from analysis and Stage I to III disease was examined independently. Over the timeframe, there was a shift amongst those without distant metastases towards a higher proportion of Stage I cancers in later years (17% EPrS vs 28% PoS, p<0.001) (Table 2.2).

Patients with colorectal cancer diagnosed in the PoS timeframe were further examined to compare screen-detected and non screen-detected disease (Table 2.3). Patients with screen-detected disease were more likely to be younger (p<0.001), male (p<0.001), less deprived (p=0.002) and present electively (p<0.001). In addition screen-detected tumours were more

likely to be distal ($p<0.001$), of an earlier stage ($p<0.001$) and managed with a curative intent ($p<0.001$).

2.4 Discussion

This Chapter provides an overview of the changes in mode, site and stage of colorectal cancer presentation in a single geographical area over the past decade, accompanying the introduction of a national screening programme. The present study has shown a reduction in emergency presentation, a reduction in the proportion of rectal cancers and a shift amongst those without distant metastases to earlier stage at diagnosis. Furthermore, an overall increase in the proportion of patients managed with a curative intent has been identified.

Examining the impact of screening on overall TNM Stage at presentation using population-based datasets can be problematic. This is due to high numbers of patients with incomplete staging information and limited information on those with metastatic disease. For example, in a recent population study examining tumours diagnosed within and without the English Bowel Cancer Screening Programme, 25% of cases were unstaged (Morris, Whitehouse et al. 2012), similar to the present study. In addition, patients who do not have complete staging information are more likely to die closer to their time of diagnosis, implying the presence of more advanced disease (Downing, Aravani et al. 2013).

The MCN has been introduced to improve outcome in colorectal cancer through delivery of high quality care with a focus on surgical outcomes. Data is collated following local MDT discussion, therefore information on patients with metastatic disease who are managed palliatively is poorly captured. It is recognised that this limitation of the dataset is particularly true in the early cohorts. For example, only 1% of patients in the EPrS timeframe did not undergo a procedure compared to 20% of patients in PoS timeframe. Furthermore, examining Stage IV disease across the timeframe actually showed an increase from 3% (EPrS) to 9% (PoS) with a concurrent rise in unstaged disease from 13%

(EPrS) to 25% (PoS) (data not presented). However, this clearly identifies a failure in capture of metastatic or incompletely staged patients of the MCN dataset.

Therefore, in order to maintain data quality when examining stage, the present study chose to focus only on those without distant metastases. When this was considered separately, a clear trend towards larger proportions of node-negative and Stage I disease following screening introduction was seen. It has been reported that tumours detected through the screening pathway are of an earlier stage compared to non-screen detected and the present study supports this finding (Morris, Whitehouse et al. 2012; Roxburgh, McTaggart et al. 2013). In addition, despite only accounting for 18% of all tumours diagnosed, an overall impact on the population has been noted. Such a change may well be associated not only with the test itself, but with an overall improvement in the knowledge and attitudes of the population with the widespread publication of screening information. However, there should be a degree of caution used in interpreting this stage-shift amongst those without distant metastases, as it has been shown that the proportion of Stage I disease may well reduce with successive screening rounds (Steele, McClements et al. 2009). Hence, further work examining the impact on stage at a population level as subsequent rounds of screening occur is required for clarification.

Emergency presentation has long been associated with both poorer short-term (Anderson, Hole et al. 1992; McArdle and Hole 2004) and long-term outcomes (McMillan, McArdle et al. 2010; Gunnarsson, Holm et al. 2011). This disparity has been shown to exist even when node-negative disease is examined independently (Oliphant, Mansouri et al. 2014). The reason for this poorer outcome appears multifactorial incorporating elements such as tumour characteristics (Wong, Jalaludin et al. 2008), pre-operative patient morbidity (Skala, Gervaz et al. 2009), use of a specialist surgeon (Biondo, Kreisler et al. 2010) and the presence of an elevated host pre-operative systemic inflammatory response (Crozier,

Leitch et al. 2009). There is evidence from the Nottingham gFOBt screening trial that emergency presentation is reduced in a population undergoing screening (Scholefield, Robinson et al. 1998). In addition, the Coventry arm of the population pilot study reported similar findings, with emergency admissions from colorectal cancer reducing from 29% in 1999 to 16% in 2004, with a concomitant improvement in 30-day mortality, following screening introduction (Goodyear, Leung et al. 2008). Interestingly, the present study showed a reduction in the proportion of emergency presentation prior to the introduction of screening, however little change during its rollout and widespread adoption. It therefore questions the impact that screening itself has had on overall emergency presentation in our geographical area. This is in keeping with a recently published cohort study that has shown that emergency admissions are reduced when comparing participants and non-participants in screening, however remain similar comparing cohorts invited and not invited to screening (Libby, Brewster et al. 2014). Therefore, it appears that it is participation and not invitation that is the key determinant in reducing emergency admissions.

In the present study, only 18% of all patients in the PoS cohort presented through the screening programme. This is on the background of an overall uptake of screening in our geographical region of 52% with lower uptake in the most deprived cohorts. Higher rates of emergency presentation are associated with socioeconomic deprivation and elderly age (Gunnarsson, Ekholm et al. 2013). However, such deprived patients are less likely to choose to participate in screening (Steele, Kostourou et al. 2010; von Wagner, Baio et al. 2011) and patients over the age of 74 years are currently not routinely invited to screening. Moreover, it has previously been shown that those patients who are socioeconomically deprived have a worse outcome following a diagnosis of colorectal cancer (Kelsall, Baglietto et al. 2009; Oliphant, Nicholson et al. 2013). Hence, the current screening programme may underserve the very people who do worse. Efforts to improve uptake of the programme should therefore be made to target such subgroups. One of the concerns

raised regarding screening is that it may widen the gap in outcomes that has been created by socioeconomic deprivation and this may be associated with its effect on the rate of emergency presentation.

The strengths of the present study are its size and the prospectively collected core dataset including data on emergency presentation. It is recognised that there are issues with utilising population-based databases such as missing data. Nevertheless, such prospective datasets provide an opportunity to examine overall trends. Furthermore there are additional tumour and host variables that determine outcome independent of TNM stage that would be of interest to explore, however, these were not collected prospectively over the time period. This is particularly relevant for Stage II disease where outcome can be varied (Roxburgh, McMillan et al. 2014; Park, Watt et al. 2015). Further work with mature follow-up and detailed tumour and host information is required to assess the impact on outcome particularly in Stage II disease.

A further limitation is utilising data over a decade, where staging modalities may have altered. For example, changes in the sensitivity of CT in detecting metastatic disease or changes in the approach to the pathological processing of specimens may have led to a comparative understaging of those in the earlier cohorts (i.e. a more attentive approach to lymph node examination in later years). However, such bias is difficult to avoid when examining historical data. Finally, our definition of emergency presentation includes those admitted with acute bleeding. Recently it has been reported that those patients with colorectal cancer who present with GI bleeding have a better outcome than others and as such grouping these along with colonic perforation and obstruction is suboptimal (Alexiusdottir, Snaebjornsson et al. 2013). Nevertheless, this was the definition of an emergency as coded prospectively in the dataset therefore precluded more detailed analysis.

In conclusion, examining population data from the West of Scotland over the past decade has identified that the SBoSP now accounts for 18% of all tumours encountered in clinical practice. Over the past decade, accompanying the introduction of screening, there has been a reduction in the rate of emergency presentation, a rise in the proportion of operative procedures performed with a curative intent and, in patients with no evidence of distant metastases, a shift towards an increased number of earlier stage tumours. These changes are likely to improve outcomes overall in the West of Scotland for patients presenting with colorectal cancer, however, there is a need for high quality follow-up to establish this.

Table 2.1: Temporal trends in colorectal cancer presentation with the introduction of screening

	All pts	Pre-screening Early 2003-2004	Pre-screening Late 2005-2006	Screening Introduction Early 2007-2008	Screening Introduction Late 2009-2010	Post-screening 2011-2012	p-value
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
	14 487	2380	2384	3098	3282	3343	
Age							
<50 yrs	751 (5)	129 (5)	129 (5)	172 (6)	139 (4)	182 (5)	
50 - 74 yrs	8142 (56)	1250 (53)	1368 (57)	1702 (55)	1897 (58)	1925 (58)	
≥75 yrs	5299 (37)	851 (35)	793 (33)	1202 (39)	1224 (37)	1229 (37)	0.584
Unknown	*295 (2)*	*150 (6)*	*94 (4)*	*22 (1)*	*23 (1)*	*6 (0)*	
Sex							
Female	6364 (44)	1017 (42)	1054(44)	1384 (45)	1416 (43)	1493 (45)	
Male	7827 (54)	1213 (51)	1236 (52)	1692 (55)	1843 (56)	1843 (55)	0.169
Unknown	*296 (2)*	*150 (6)*	*94 (4)*	*22 (1)*	*23 (1)*	*7 (0)*	
Deprivation category							
1 (most deprived)	4329 (30)	667 (28)	706 (30)	935 (30)	978 (30)	1043 (31)	
2	3398 (23)	545 (23)	555 (23)	732 (24)	776 (24)	790 (24)	
3	2370 (16)	364 (15)	380 (16)	529 (17)	557 (17)	540 (16)	
4	1921 (13)	307 (13)	300 (13)	406 (13)	433 (13)	475 (14)	
5 (least deprived)	2072 (14)	247 (16)	349 (15)	474 (15)	514 (16)	488 (15)	0.057
Unknown	*297 (2)*	*150 (6)*	*94 (4)*	*22 (1)*	*24 (1)*	*7 (0)*	
Presentation to surgery							
Emergency	2163 (15)	480 (20)	431 (18)	414 (13)	420 (13)	418 (13)	
Elective - symptomatic	8948 (62)	1849 (78)	1868 (78)	1910 (62)	1729 (53)	1592 (47)	
- screen-detected[a]	1200 (8)	-	-	107 (3)	486 (15)	607 (18)	<0.001[b]
Did not undergo procedure	*2056 (14)*	*30 (1)*	*56 (2)*	*624 (20)*	*642 (20)*	*704 (21)*	
Unknown	*115 (1)*	*21 (5)*	*29 (3)*	*43 (1)*	*5 (0)*	*22 (1)*	

Table 2.1: Temporal trends in colorectal cancer presentation with the introduction of screening (continued)

	All pts	Pre-screening		Screening Introduction		Post-screening	p-value
		Early	Late	Early	Late		
		2003-2004	2005-2006	2007-2008	2009-2010	2011-2012	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
	14 487	2380	2384	3098	3282	14 487	
Site of tumour							
Right Colon	4857 (34)	753 (32)	811 (34)	1048 (34)	1099 (34)	1146 (34)	
Left Colon	4827 (33)	790 (33)	736 (31)	997 (32)	1165 (35)	1139 (34)	
Rectum	4647 (32)	825 (34)	818 (34)	996 (32)	983 (30)	1025 (31)	0.001
Multiple/unknown	*156 (1)*	*12 (1)*	*19 (1)*	*57 (2)*	*35 (1)*	*33 (1)*	
Management Intent							
Curative intent	9980 (68)	1797 (76)	1744 (73)	1972 (64)	2238 (68)	2229 (67)	
Palliative procedure	1877 (13)	440 (18)	389 (16)	337 (11)	334 (10)	377 (11)	<0.001[c]
Did not undergo procedure	*2056 (14)*	*30 (1)*	*56 (2)*	*624 (20)*	*642 (20)*	*704 (21)*	
Unknown/other	*574 (4)*	*113 (5)*	*195 (8)*	*165 (5)*	*68 (2)*	*33 (1)*	

[a] Recorded from 2007 onwards
[b] Emergency vs all Elective (including screen-detected)
[c] Curative vs palliative resection

Table 2.2: Temporal trends in TNM stage of colorectal cancer at presentation with the introduction of screening (non-metastatic disease only)

		Pre-screening		Screening Introduction		Post-screening	
	All pts	Early	Late	Early	Late		
		2003-2004	2005-2006	2007-2008	2009-2010	2011-2012	p-value
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
	10400	1999	1992	2072	2118	2219	
TNM Stage							
I	2134 (17)	348 (17)	329 (17)	367 (18)	461 (22)	629 (28)	
II	4124 (40)	791 (40)	803 (40)	884 (42)	834 (40)	812 (37)	
III	4142 (43)	860 (43)	860 (43)	821 (40)	823 (39)	778 (35)	<0.001

Table 2.3: Comparison of screen-detected and non screen-detected colorectal cancer in the West of Scotland (2011-2012)

	All patients	Screen detected	Non-screen detected	
	n(%)	n(%)	n(%)	p-value
	3343	672	2671	
Age				
<50 yrs	182 (5)	1 (0)	182 (7)	
50 - 74 yrs	1925 (58)	607 (90)	1318 (49)	
≥75 yrs	1229 (37)	64 (10)	1165 (44)	<0.001
Unknown	*6 (0)*	*0 (0)*	*6 (0)*	
Sex				
Female	1493 (45)	246 (37)	1247 (47)	
Male	1843 (55)	425 (63)	1418 (53)	<0.001
Unknown	*7 (0)*	*1 (0)*	*6 (0)*	
Deprivation category				
1 (most deprived)	1043 (31)	192 (29)	851 (32)	
2	790 (24)	150 (22)	640 (24)	
3	540 (16)	97 (14)	443 (17)	
4	475 (14)	115 (17)	360 (14)	
5 (least deprived)	488 (15)	117 (17)	371 (14)	0.002
Unknown	*7 (0)*	*1 (0)*	*6 (0)*	
Site of tumour				
Right Colon	1146 (34)	171 (25)	975 (37)	
Left Colon	1139 (34)	284 (42)	855 (32)	
Rectum	1025 (31)	214 (32)	811 (30)	<0.001
Multiple/unknown	*33 (1)*	*3 (0)*	*30 (1)*	
Management Intent				
Curative intent	2229 (67)	600 (89)	1629 (61)	
Palliative procedure	377 (11)	27 (4)	350 (13)	<0.001[a]
Did not undergo procedure	*704 (21)*	*40 (6)*	*664 (25)*	
Unknown/other	*33 (1)*	*5 (1)*	*28 (1)*	
Presentation to surgery				
Emergency	418 (13)	12 (2)	406 (15)	
Elective	2199 (65)	607 (90)	1592 (60)	<0.001[b]
Did not undergo procedure	704 (21)	*40 (6)*	*664 (25)*	
Unknown	*22 (1)*	*13 (2)*	*9 (0)*	
TNM Stage				
I	629 (19)	256 (38)	373 (14)	
II	812 (24)	164 (24)	648 (24)	
III	778 (23)	155 (23)	623 (23)	
IV	295 (9)	24 (4)	271 (10)	<0.001
Unknown/other	*829 (25)*	*73 (11)*	*756 (28)*	

[a] Curative vs palliative resection
[b] Emergency vs elective presentation

3 THE IMPACT OF AGE, SEX AND SOCIOECONOMIC DEPRIVATION ON OUTCOMES IN A COLORECTAL CANCER SCREENING PROGRAMME

3.1 Introduction

There is evidence that an individuals risk of colorectal cancer is associated with socioeconomic deprivation, in particular in males, with those in the least deprived categories having a 20% lower incidence compared with those in the most deprived (Oliphant, Brewster et al. 2011). There is also evidence that following a diagnosis of colorectal cancer, those who are more socioeconomically deprived have both a poorer cancer specific and overall survival (Hole and McArdle 2002).

As discussed in the previous chapter, bowel screening programmes utilising both gFOBt and FIT have been introduced across the UK and have seen overall participation rates of over 50% (Steele, McClements et al. 2009; von Wagner, Baio et al. 2011). Within this, however, participation rates may vary widely across demographic groups, with those who are male, younger, more deprived and more ethnically diverse reported less likely to engage in the process (Steele, Kostourou et al. 2010; von Wagner, Baio et al. 2011). This has added further weight to the suggestion that such individuals may gain a disproportionately low share of the survival benefits from screening (Whynes, Frew et al. 2003).

The Scottish Bowel Screening Programme (SBoSP) was introduced in a staged manner across Scotland beginning in 2007 and was introduced in NHS Greater Glasgow and Clyde in April 2009. In particular, this geographical area is recognised to be one in which there is a high incidence of multiple deprivation. For example, NHS Greater Glasgow and Clyde encompasses an area that includes 49% of the most deprived areas in Scotland. This is the

highest proportion of any health board in Scotland and can be compared to the second highest proportion which is 7% in Edinburgh (SIMD 2009).

The aim of the present study was to examine, in an area of multiple deprivation, the impact of age, sex and socioeconomic deprivation not only on uptake, but throughout all stages of the screening process.

3.2 Materials and methods

Beginning in April 2009 all males and females between the age of 50 and 74 and registered with a General Practitioner (GP) in NHS Greater Glasgow & Clyde were identified via their Community Health Index (CHI) and invited to participate in the SBoSP. Each participant was initially sent a pre-notification letter advising them that they would be receiving an invite to participate in the screening programme. Each participant was then sent a gFOBt kit and asked to provide 2 samples from 3 separate faecal specimens. The screening algorithm of the SBoSP has been covered in Chapter 1. Following a positive test result, individuals were pre-assessed, either face-to-face or following telephone consultation, by a bowel screening endoscopy nurse and then referred on for colonoscopy if this was deemed suitable. If colonoscopy was unsuccessful then further bowel imaging by barium enema or CT pneumocolonography was attempted. As screening is biennial, two years worth of test invitations were taken to comprise one complete screening round.

Participant details were obtained from a prospectively maintained database held by the Public Health Screening Unit in NHS Greater Glasgow and Clyde. In order to establish a robust dataset, data on endoscopic findings and pathological diagnosis was obtained retrospectively from clinical information systems on a case-by-case basis. These results formed the basis of the analysis. The presence of uncomplicated diverticulosis and hyperplastic polyps was noted as normal findings. The presence of colitis/proctitis, angiodysplasia, or haemorrhoids were classified as non-neoplastic pathology as a cause of the positive test.

Deprivation category was calculated using the Scottish Index of Multiple Deprivation 2009 (SIMD) which is an index of relative deprivation combining multiple detailed indicators across 7 domains (SIMD 2009). The overall index is a weighted rank for each of these domains; income (28%), employment (28%), health (14%), education, skills and training

(14%), geographic access (9%), crime (5%) and housing (2%). Based on this weighted rank, the 6505 postcodes in Scotland are ranked in order of deprivation. Each postcode represents a small geographical area containing around 750 people. Quintiles of deprivation were used to assign individuals a relative deprivation category based on their postcode at time of colonoscopy with the first quintile representing the most deprived and the fifth quintile, the least deprived. Therefore, those in the first quintile, the most deprived, were likely to have higher levels of poverty, unemployment and poorer health than those in the fifth quintile, who were least deprived.

In those individuals in whom a pathological diagnosis of dysplastic polyps was reached, they were classified as being of a low risk, intermediate risk or high risk of subsequent development of colorectal cancer as per British Society of Gastroenterology (BSG) guidelines (Atkin and Saunders 2002). (low risk; 1 to 2 polyps <1cm: intermediate risk; 3-4 polyps <1cm or $\geq$ 1 polyp $\geq$ 1cm: high risk; $\geq$5 polyps or $\geq$ 3 polyps of which $\geq$ 1 is $\geq$ 1cm). Low risk polyps were termed non-significant and intermediate or high risk polyps termed significant.

In those individuals in whom a diagnosis of colorectal cancer was reached, initial staging for comparison was following endoscopic and imaging modalities. Subsequent, pathological classification in those who underwent operations was by the standard TNM (version 5) classification (Sobin and Fleming 1997) based on histological resection of specimens. Individuals in whom a polyp cancer was considered to be completely excised endoscopically and hence did not undergo further colonic resection, were presumed to be node negative and classified as Stage I.

The positive predictive value (PPV) for detecting cancer was defined as the number of individuals in whom a cancer was detected divided by the number of individuals undergoing colonoscopy. The PPV for neoplasia was defined as the number of individuals

in whom a cancer or dysplastic polyp was identified divided by the number of individuals undergoing colonoscopy and the PPV for significant neoplasia was the number of individuals with either a cancer or significant polyps divided by the number of individuals undergoing colonoscopy. The cancer detection rate was defined as the number of individuals detected with cancer divided by the number who responded to screening test invitation.

Statistical analysis

Associations between categorical variables were examined using χ^2 tests for linear trend unless otherwise specified. Multivariate analysis was carried out using binary logistical regression. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA)

3.3 Results

From April 2009 to March 2011 inclusive, 395 096 individuals were invited to participate in screening in whom full details on age, sex and deprivation were available for 394 117 (99.8%) which were included for analysis. 192 294 (48.8%) were in the two most deprived quintiles of deprivation and 192 312 (48.9%) were male. The demographic details are shown in Table 1 and a flow diagram of the cohort is outlined in Figure 3.1.

Outcome of screening invitation

Of the 394 117 people invited, 204 139 (51.8%) chose to take up the test (Table 3.1). Uptake was higher in older individuals (45.8% vs 54.6% vs 55.3%, $p<0.001$), females (55.4% vs 48.1%, $p<0.001$), and those who were less socioeconomically deprived (62.7% least deprived vs 42.0% most deprived, $p<0.001$). Due to significant interrelationships between age, sex and deprivation in the cohort invited to screening, multivariate analysis was undertaken. The relationships between age, sex and deprivation identified on univariate analysis remained significant ($p<0.001$).

Outcome of screening test

Of the 204 139 who took up the test, 6 079 (3.0%) tested positive (Table 3.2). Positivity rates were higher with advancing age (2.0% vs 2.7% vs 4.1%, $p<0.001$), in males (3.8% vs 2.3%, $p<0.001$), and in those who were more deprived (4.2% most deprived vs 1.9% least deprived, $p<0.001$). Due to a significant interrelationship between age and sex in the cohort responding to the screening invitation, multivariate analysis was undertaken. The relationships with both increasing age and increasing deprivation, and higher positivity rates, remained significant ($p<0.001$).

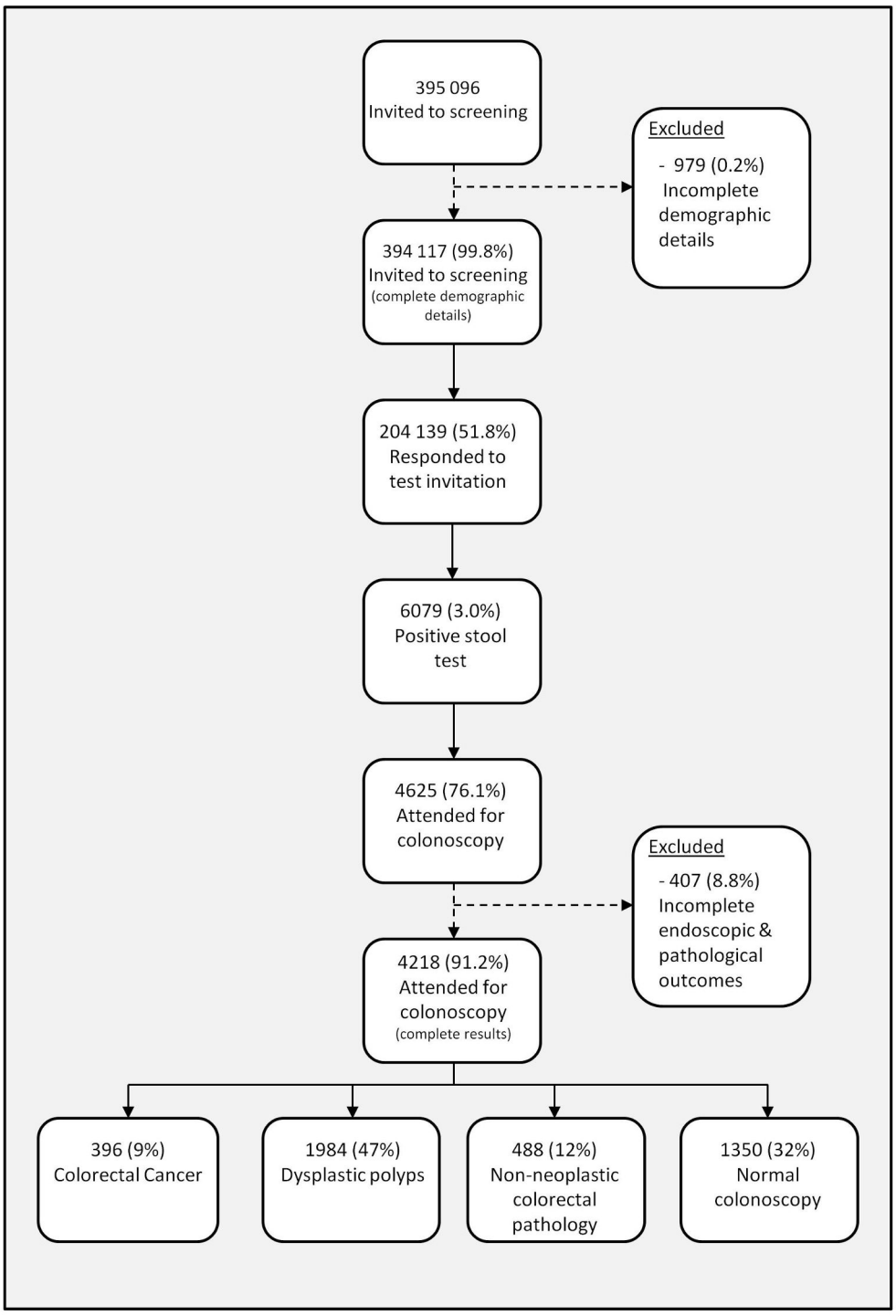


Figure 3.1: Outcomes of the first round of screening in NHS GG&C

Attendance for colonoscopy

Of the 6 079 positive cases, following pre-assessment, 4 625 (76.1%) individuals attended for colonoscopy (Table 3.3). Failure to attend for colonoscopy was not associated with age or sex. However, it was associated with deprivation (80.0% least deprived vs 73.3% most deprived, $p<0.001$).

Outcome of colonoscopy

Cancer

Of the 4 625 individuals who underwent colonoscopy, full endoscopic and pathological results were available for 4 218 (91.2%) which were included for analysis. Cancer was detected in 396 individuals (9.4%) (Table 3.4). Increasing age (5.3% vs 8.1% vs 11.9%, $p<0.001$) and male sex (10.5% vs 7.7%, $p=0.002$) were associated with higher PPVs of cancer at colonoscopy. Despite the highest test positivity rates in the most deprived individuals, being less deprived was actually associated with a higher PPV for cancer (10.5% least deprived vs 7.8% most deprived, $p=0.003$). Due to significant interrelationships between age, sex and deprivation within those who underwent colonoscopy, multivariate analysis was undertaken. Older age and male sex remained significant (both $p<0.05$), however the relationship between reduced deprivation and a higher likelihood of cancer remained significant in those in the 3 least deprived quintiles of deprivation only.

Of the 396 individuals with cancer, completing staging information was present in 379 (95.7%). Of these, 181 (48.1%) tumours were Stage I, 80 (21.1%) were Stage II, 93 (24.5%) were Stage III and 25 (6.6%) were Stage IV. There was no effect of age, sex and deprivation on the stage of cancer detected through screening.

Dysplastic polyps

Of the 4 218 with colonoscopy results, 1 984 (47.0%) had dysplastic polyps detected (Table 3.5). Of the 1 984 individuals with dysplastic polyps, 662 (33.4%) individuals had non-significant polyps, and 1322 (66.6%) individuals had significant polyps (937 (70.8%) were intermediate risk and 385 (29.1%) were high risk). This gave a PPV for neoplasia (cancer or polyp) of 56.4% and a PPV for significant neoplasia (significant polyp or cancer) of 40.7% at colonoscopy. Increasing age (43.6% vs 56.3% vs 62.0%, $p<0.001$: 30.2% vs 40.2% vs 45.6%, $p<0.001$) and male sex (66.0% vs 42.5%, $p<0.001$: 48.4% vs 29.5%, $p<0.001$) were associated with higher PPVs of both of these measures. Again, despite the highest test positivity rate in the most deprived individuals, being less deprived was actually associated with a higher PPV for both neoplasia and significant neoplasia (58.7% least deprived vs 53.3% most deprived, $p=0.016$: 45.0% least deprived vs 36.9% most deprived, $p<0.001$). There was no apparent association between age and deprivation noted, therefore the data was further stratified by sex only. The relationship with increasing age and a higher PPV for neoplasia and significant neoplasia age remained ($p<0.001$). The relationship between deprivation and lower PPV for both neoplasia and significant neoplasia remained only in males ($p<0.005$).

Within the 1 984 individuals with dysplastic polyps, the presence of significant polyps was associated with being male (68.3% vs 62.7%, $p=0.015$) and being less deprived (71.5% least deprived vs 63.9% most deprived, $p=0.006$) (Table 6). There was no association with age noted ($p=0.452$).. Within those with significant polyps, there were no significant interrelationships noted between age, sex and socioeconomic deprivation therefore multivariate analysis was not undertaken.

Non-neoplastic pathology

Of the 4 218 with colonoscopy results, 488 (11.6%) had non-neoplastic colorectal pathology identified as being a cause for the positive test result (Table 3.5). Younger age (14.9% vs 11.6% vs 10.1%, p<0.001), and being female (14.2% vs 9.8%, p<0.001) was associated with an increased likelihood of non-neoplastic colorectal pathology being identified. No association with deprivation was found (p=0.935). The data was further stratified by sex and the relationship with younger age and higher likelihood of having non-neoplastic colorectal pathology identified remained significant (p<0.05).

Normal colonoscopy

Of the 4 219 with colonoscopy results, 1 350 (32.0%) had a normal colonoscopy (Table 3.5). Decreasing age (41.5% vs 32.0% vs 27.9%, p<0.001), female sex (43.3% vs 24.3%, p<0.001) and increasing deprivation (34.9% least deprived vs 29.6% most deprived, p=0.012) were all associated with a higher likelihood of a normal colonoscopy. There was no apparent association between age and deprivation noted, therefore the data was further stratified by sex only. The relationship between younger age and a higher likelihood of a normal colonoscopy remained (p<0.001). No relationship with deprivation was seen in females, and a non-significant trend in males was seen (23.8% least deprived vs 27.4% most deprived, p=0.099).

Cancer Detection rate

The cancer detection rates was 0.19% overall. This was significantly higher in males (0.29% vs 0.12%, p<0.001), older individuals (0.08% vs 0.15% vs 0.33%, p<0.001) and more deprived individuals (0.22% most deprived vs 0.15% least deprived, p=0.006). There was an apparent association between age and deprivation noted, therefore the data was further stratified by both sex and age groups. The relationship between both increasing age and increasing deprivation, and higher cancer detection rates remained significant (all

$p<0.05$). Converting the cancer detection rate to a number needed to test to identify 1 patient with colorectal cancer yielded an overall value of 515 individuals. This was lower with advancing age (1289 individuals vs 655 individuals vs 301 individuals) and male sex (351 males vs 844 females). The number needed to test was lower with more deprived individuals (446 most deprived vs 669 least deprived).

3.4 Discussion

The results of the present study show that age, sex and socioeconomic deprivation have a significant impact throughout the colorectal cancer screening pathway. Males were less likely to respond to screening, more likely to test positive and more likely to have cancer diagnosed following a positive test. This was also the case with older individuals. Furthermore, those who were more deprived were less likely to respond to screening, more likely to test positive, however, were more likely to fail to proceed to colonoscopy and less likely to have cancer or polyps diagnosed at colonoscopy. Therefore, this study suggests that strategies aimed at improving participation of deprived individuals in colorectal cancer screening should be directed at all stages of the screening process and not just uptake of the test.

Overall, our uptake of the screening test (52%) was slightly below both figures from the first round of the Scottish pilot study and first round of the English screening programme (Steele, McClements et al. 2009; Logan, Patnick et al. 2012). This is despite individuals in our area being sent a pre-notification letter that has previously been shown to improve participation rates, something that was not done in the other studies (Libby, Bray et al. 2011). The lower overall uptake may be due to the high level of deprivation in our population when compared to both the Scottish pilot study and the English figures (32% of our population invited to screening were in the most deprived quintile of deprivation compared to 10% in the most deprived quintile in the Scottish pilot study and 20% in the most deprived quintile in the English programme). Within this, a poorer response to invitations in younger individuals, males, and those who were more deprived was also seen. This effect appeared cumulative, for example younger, males who were most deprived had a 34% response rate compared to older, females, who were least deprived who had a response rate of 69%. The gradient of disparity in response to screening invite

was largest in the socioeconomically deprived highlighting the important role that deprivation has determining the uptake of a colorectal cancer programme.

In a recent randomised control trial, a multifaceted intervention was instigated in a deprived population utilising, amongst other means, an automated telephone and text reminder system in order to try and improve FOBt uptake (Baker, Brown et al. 2014). In the intervention group, uptake was increased from 37% to above 80%. The authors suggested that targeted intervention of at risk low uptake groups using technologies such as this could be feasible. Due to cost constraints such technologies are not routinely employed within the SBoSP however, it may be worth considering such tools in our most deprived areas if uptake is to be increased.

It was also of note that deprivation was the only variable associated with failing to proceed to colonoscopy following a positive result. The reasons for failing to proceed to colonoscopy may either be participant factors (choosing not to participate) or medical factors (participant not being fit enough to proceed). Indeed, overall health is a facet of deprivation and hence more deprived individuals may be less likely to be as fit to undergo a colonoscopy as less deprived individuals. It has already been noted that one of the disadvantages of screening is the anxiety and stress of a positive result in an otherwise asymptomatic individual and in an individual that has a positive screening test and is not fit enough to proceed to colonoscopy, this effect may be magnified (Hewitson, Glasziou et al. 2008). Our study reinforces both recent results from the English screening programme and results from the Scottish pilot study that have shown increased rates of non-attendance in those who are more socioeconomically deprived (Steele, Kostourou et al. 2010; Morris, Baio et al. 2012). As these previous studies did not include those deemed unsuitable for colonoscopy, uptake rates were higher, however it is worth noting that the gradient in disparity associated with deprivation was smaller than the results of the present study. One

explanation may be the differing spectrum of deprivation in different geographical areas. It is important that further work focuses on the specific barriers to proceeding to colonoscopy.

The positivity rate (3%), and PPV for cancer at colonoscopy (9%) were similar to previously reported figures from both Scotland and England (Steele, McClements et al. 2009; Logan, Patnick et al. 2012). However, within this, wide variations throughout the demographics were noted. The higher cancer detection rate found in older, males, who were more deprived by this study was expected, as this is indicative of the overall incidence of the disease. (Cancer Research UK) However, it was surprising that there was an inverse relationship between the PPV for cancer at colonoscopy and deprivation. The results of the present study found a higher PPV for cancer at colonoscopy in those who were less deprived. The reasons for this remain unclear. It is thought that not all screen detected cancers are asymptomatic, and that individuals who choose to take up screening are more likely to have lower gastrointestinal symptoms (Harmston, Akwei et al. 2010). It has been suggested that rather than only identifying occult disease, screening represents another pathway for symptomatic individuals to choose to present.

Therefore, one plausible explanation is that the lower PPV for cancer at colonoscopy exhibited by those who were more deprived was related to the fact that they had a higher incidence of other non-neoplastic colorectal pathology. While not directly related to cancer detection, had a higher rate of non-neoplastic pathology, such as colitis, be detected in this subpopulation then it may be an added benefit of screening. However, the results of this study do not support this theory. The lower PPV for cancer appeared to be due to a higher number of normal colonoscopies in the more deprived group, which can be viewed as a ‘true’ false positive rate of the test.

False positives with gFOBt can be due to upper gastrointestinal (GI) causes or dietary factors, although a link with either of these and socio-economic deprivation has not previously been demonstrated (Bretthauer 2011). In a study by Rockey et al. healthy volunteers were given small volumes of their own blood to ingest. gFOBt's and FIT's were subsequently examined, with the gFOBt's found be positive and the FIT's negative. The positivity rates of gFOBt's increased with increasing amounts of ingested blood suggesting that a relationship between blood in the upper GI tract and positivity exists (Rockey, Auslander et al. 1999). Indeed, there is ongoing debate as to role of upper GI endoscopy in patients who are gFOBt positive and colonoscopy negative (Allard, Cosby et al. 2010). However, the applicability of this to the present study is not clear. A substantial number of patients in the present study will only have been weakly gFOBt positive and will have proceeded to colonoscopy following a subsequent positive FIT. Further work is therefore required to explore the disparity between a higher test positivity rate and a lower PPV of cancer at colonoscopy associated with deprivation within the context of a reflex gFOBt/FIT screening programme.

The PPV for detecting cancer is not the only significant feature of the screening test, as the elimination of pre-cancerous dysplastic polyps is also important to monitor. In fact, a high adenoma pick up rate has been shown to reduce the incidence of colorectal cancer within a screened population, and the removal of dysplastic polyps at colonoscopy has recently been shown to reduce cancer-specific mortality in the long term (Mandel, Church et al. 2000; Zauber, Winawer et al. 2012). The fact that our findings were consistently observed across the PPV for detecting cancer, and both the PPV for neoplasia and significant neoplasia is further validation of the impact of age, sex and deprivation and to date has not been previously reported. Moreover, the present study is able to examine in detail different types of dysplastic polyps. It would be overly simplistic to group all dysplastic polyps as

being of equal relevance within a screening programme and the present study has sufficiently large numbers to allow such a subanalysis to take place.

This is a retrospective study using a prospectively maintained database and has a number of limitations. First of all, the proportion of patients in the study who had previously undergone colonoscopy or other lower GI investigation is unknown. This may have affected both an individuals' attitude towards engaging in the screening process and the likelihood of finding significant pathology at colonoscopy. Indeed, the multicentre UK Flexible Sigmoidoscopy Trial recruited patients aged 55 to 64 years in NHS GG&C up to March 1999 and there may be some crossover between individuals included in the present study and this previous trial (Atkin, Cook et al. 2002). However, the proportion of such individuals is likely to be less than 10%. Furthermore the present study is not able to assess reasons for non-participation or outcomes in those who chose not to participate. Assessing outcomes, such as a subsequent colonoscopy or cancer diagnosis, in non-responders or those who tested negative requires complex data linkage with population based datasets and such information was not available in the present study. In addition, a positive test in the present study actually represents the outcome from three separate screening pathways; strongly positive gFOBt, positive FIT following a weak gFOBt or a positive FIT following a spoiled/untestable gFOBt. There was limited data on the type of positive test for each individual (either gFOBt or FIT) or compliance with FIT in those who tested weakly positive on gFOBt, and therefore this was not able to be included in analysis.

In summary, this data demonstrates that there are wide variations in uptake and outcomes with colorectal cancer screening in its current reflex gFOBt/FIT format associated with age, sex and socioeconomic deprivation. However, deprivation should be highlighted as the only variable that has a consistent impact throughout all stages of the process. Strategies aimed at improving participation of deprived individuals in colorectal cancer

screening should be directed at all stages of the screening process and not just uptake of the screening test.

Table 3.1: Outcome of screening invitation within the SBoSP in NHS GG&C

	All individuals invited to screening n (%)	Responders n (%)	Non-responders n (%)	% Responders	p-value	Multivariate analysis O.R. (95% CI)	p-value
	394 117	204 139	189 978	52%			
Age							
≤55y	135 145 (34%)	61 858 (30%)	73 287 (39%)	45%		1.00	
56y-64y	126 032 (32%)	68 797 (34%)	57 235 (30%)	55%		1.41 (1.39 – 1.44)	<0.001
≥ 65y	132 940 (34%)	73 484 (36%)	59 456 (31%)	55%	<0.001	1.47 (1.45 – 1.49)	<0.001
Sex							
Male	192 912 (49%)	92 723 (45%)	100 189 (53%)	48%		1.00	
Female	201 205 (51%)	111 416 (55%)	89 789 (47%)	55%	<0.001	1.34 (1.32 – 1.35)	<0.001
Deprivation quintile							
1 (most deprived)	125 263 (32%)	52 604 (26%)	72 659 (38%)	42%		1.00	
2	67 031 (17%)	32 838 (16%)	34 193 (18%)	49%		1.32 (1.30 – 1.35)	<0.001
3	64 237 (16%)	34 984 (17%)	29 253 (15%)	54%		1.65 (1.62 – 1.68)	<0.001
4	58 687 (15%)	34 230 (17%)	24 457 (13%)	58%		1.95 (1.91 – 1.99)	<0.001
5 (least deprived)	78 899 (20%)	49 483 (24%)	29 416 (16%)	63%	<0.001	2.34 (2.29 – 2.38)	<0.001

Table 3.2: Outcome of screening test within the SBoSP in NHS GG&C

	All individuals responding to screening invite	Positive screening test	Negative screening test	% Positive	p-value	Multivariate analysis	p-value
	n (%)	n (%)	n (%)			O.R. (95% CI)	
	204 139	6 079	198 060	3%			
Age							
≤55y	61 858 (30%)	1 256 (21%)	60 602 (31%)	2%		1.00	
56y-64y	68 797 (34%)	1 842 (30%)	66 955 (34%)	3%		1.35 (1.26 – 1.45)	<0.001
≥ 65y	73 484 (36%)	2 981 (49%)	70 503 (36%)	4%	<0.001	2.07 (1.93 – 2.21)	<0.001
Sex							
Male	92 723 (45%)	3 560 (59%)	89 163 (45%)	4%		1.00	
Female	111 416 (55%)	2 519 (41%)	108 897 (55%)	2%	<0.001	0.57 (0.54 – 0.60)	<0.001
Deprivation quintile							
1 (most deprived)	52 604 (26%)	2 237 (37%)	50 367 (25%)	4%		1.00	
2	32 838 (16%)	1 137 (19%)	31 701 (16%)	3%		0.80 (0.75 – 0.86)	<0.001
3	34 984 (17%)	989 (16%)	33 995 (17%)	3%		0.65 (0.60 – 0.70)	<0.001
4	34 230 (17%)	766 (13%)	33 464 (17%)	2%		0.51 (0.47 – 0.56)	<0.001
5 (least deprived)	49 483 (24%)	950 (16%)	48 533 (25%)	2%	<0.001	0.44 (0.40 – 0.47)	<0.001

Table 3.3: Attendance for colonoscopy within the SBoSP in NHS GG&C

	All individuals with a positive screening test	Attended for colonoscopy	Did not attend for colonoscopy	% Attenders	p-value
	n (%)	n (%)	n (%)		
	6 079	4625	1454	76%	
Age					
≤55y	1 256 (21%)	961 (21%)	295 (20%)	77%	
56y-64y	1 842 (30%)	1 416 (31%)	426 (29%)	77%	
≥ 65y	2 981 (49%)	2 248 (49%)	733 (50%)	75%	0.331
Sex					
Male	3 560 (59%)	2 732 (59%)	828 (57%)	77%	
Female	2 519 (41%)	1 893 (41%)	626 (43%)	75%	0.152
Deprivation quintile					
1 (most deprived)	2 237 (37%)	1 639 (35%)	598 (41%)	73%	
2	1 137 (19%)	868 (19%)	269 (19%)	76%	
3	989 (16%)	764 (17%)	225 (16%)	77%	
4	766 (13%)	594 (13%)	172 (12%	78%	
5 (least deprived)	950 (16%)	760 16%)	190 (13%)	80%	<0.001

Table 3.4: Detection of cancer at colonoscopy within the SBoSP in NHS GG&C

	All individuals with a colonoscopy result n (%)	Cancer n (%)	Not cancer n (%)	% Cancer	p-value	Multivariate analysis O.R. (95% CI)	p-value
	4 218	396	3 822	9%			
Age							
≤55y	880 (21%)	47 (12%)	833 (22%)	5%		1.00	
56y-64y	1 289 (31%)	105 (27%)	1 184 (31%)	8%		1.53 (1.08 – 2.19)	0.018
≥ 65y	2 049 (49%)	244 (62%)	1 805 (47%)	12%	<0.001	2.38 (1.72 – 3.29)	0.001
Sex							
Male	2 506 (59%)	264 (67%)	2 242 (59%)	11%		1.00	
Female	1 712 (41%)	132 (33%)	1 580 (41%)	8%	0.002	0.73 (0.58 – 0.90)	0.004
Deprivation quintile							
1 (most deprived)	1516 (36%)	118 (30%)	1 398 (37%)	8%		1.00	
2	791 (19%)	67 (17%)	724 (19%)	8%		1.06 (0.78 – 1.45)	0.710
3	676 (16%)	74 (19%)	602 (16%)	11%		1.42 (1.05 – 1.94)	0.025
4	530 (13%)	63 (16%)	467 (12%)	12%		1.60 (1.15 – 2.21)	0.005
5 (least deprived)	705 (17%)	74 (19%)	631 (17%)	10%	0.003	1.36 (1.00 – 1.85)	0.050

Table 3.5: Complete outcomes of colonoscopy within the SBoSP in NHS GG&C

	All individuals at colonoscopy n (%)	Colorectal Cancer n (%)	Dysplastic polyps n (%)	Non-neoplastic colorectal pathology[a] n (%)	Normal colonoscopy n (%)	p-value
	4 218	396 (9%)	1 984 (47%)	488 (12%)	1 350(32%)	
Age						
≤55y	880 (21%)	47 (12%)	337 (17%)	131 (27%)	365 (27%)	
56y-64y	1 289 (31%)	105 (27%)	621 (31%)	150 (31%)	413 (31%)	
≥ 65y	2 049 (49%)	244 (62%)	1 026 (52%)	207 (42%)	572 (42%)	<0.001
Sex						
Male	2 506 (59%)	264 (67%)	1 389 (70%)	245 (50%)	608 (45%)	
Female	1 712 (41%)	132 (33%)	595 (30%)	243 (50%)	742 (55%)	<0.001
Deprivation quintile						
1 (most deprived)	1 516 (36%)	118 (30%)	690 (35%)	179 (37%)	529 (39%)	
2	791 (19%)	67 (17%)	395 (20%)	82 (17%)	247 (18%)	
3	676 (16%)	74 (19%)	319 (16%)	89 (18%)	194 (14%)	
4	530 (13%)	63 (16%)	240 (12%)	56 (12%)	171 (13%)	
5 (least deprived)	705 (17%)	74 (19%)	340 (17%)	82 (17%)	209 (16%)	0.001

[a]Includes patients with colitis/proctitis, angiodysplasia and haemorrhoids

Table 3.6: The effect of age, sex and deprivation on the likelihood of significant polyps at colonoscopy the SBoSP in NHS GG&C

	All individuals with dysplastic polyps	Significant polyps (intermediate/high-risk)	Non-significant polyps (low-risk)	p-value
	n (%)	n (%)	n (%)	
	1 984 (47%)	1 322 (67%)	662 (33%)	
Age				
≤55y	337 (17%)	219 (17%)	118 (18%)	
56y-64y	621 (31%)	413 (31%)	208 (31%)	
≥ 65y	1 026 (52%)	690 (52%)	336 (51%)	0.452
Sex				
Male	1 389 (70%)	949 (72%)	440 (67%)	
Female	595 (30%)	373 (28%)	222 (34%)	0.015
Deprivation quintile				
1 (most deprived)	690 (35%)	441 (33%)	249 (38%)	
2	395 (20%)	259 (20%)	136 (21%)	
3	319 (16%)	208 (16%)	111 (17%)	
4	240 (12%)	171 (13%)	69 (10%)	
5 (least deprived)	340 (17%)	243 (18%)	97 (15%)	0.006

4 THE USE OF FLEXIBLE SIGMOIDOSCOPY FOLLOWING A POSITIVE FAECAL OCCULT BLOOD TEST WITHIN A BOWEL SCREENING PROGRAMME: THEORETICAL EFFECT ON NEOPLASIA DETECTION

4.1 Introduction

The current method of screening in the Scotland utilises the gFOBt to identify individuals who are subsequently referred on for colonoscopy. In addition, faecal immunochemical tests (FIT) are used in individuals with weakly positive results or in those with a spoiled test. Both the sensitivity and specificity of these, as screening tests, are low. In addition, response rates to invitation for screening nationwide are just over 50% (von Wagner, Baio et al. 2011). Furthermore, not all those that test positive are willing, or medically fit enough to undergo a full colonoscopy. It has also been noted that cancers detected through a gFOBt bowel screening programme may be disproportionately found in the left side of the colon (Logan, Patnick et al. 2012; Steele, McClements et al. 2012). Therefore, it was hypothesised that initial endoscopic examination of the left side of the colon only in gFOBt or FIT positive patients may be preferable and may not compromise screening efficacy.

There has been considerable interest in utilising flexible sigmoidoscopy as a primary screening tool for colorectal cancer and there is evidence that it can reduce both the incidence of colorectal cancer and cancer-specific mortality (Atkin, Edwards et al. 2010). This is based on the premise that approximately 60% of all neoplastic colonic pathology lies distal to the splenic flexure. In trials assessing the use of flexible sigmoidoscopy, those with significant polyps or cancer in the left side of the colon would progress for full colonoscopy (Atkin, Kralj-Hans et al. 2010). Flexible sigmoidoscopy is thought to be a more cost effective and acceptable screening test allowing higher throughput compared with colonoscopy and has recently been introduced as an adjunct to gFOBt as part of the

English bowel screening programme with a pilot study underway in Scotland assessing a similar plan.

The present study includes participants who tested positive on gFOBt or FIT and who underwent colonoscopy in the first round of the Scottish Bowel Screening Programme (SBoSP) in NHS Greater Glasgow & Clyde (NHS GG&C). The study aims to compare the detection rate of colonic adenomas/adenocarcinomas if a theoretical flexible sigmoidoscopy-first protocol was to be used as the diagnostic tool compared with full colonoscopy.

4.2 Materials and methods

Beginning April 2009 all males and females between the ages of 50 and 74 and registered with a GP in NHS GG&C were identified via their Community Health Index (CHI) and invited to participate in the SBoSP. Each participant was sent a gFOBt kit and asked to provide two samples from three separate faecal specimens. The gFOBt/FIT testing process of the SBoSP has been described fully in Chapter 1. Following a positive result screening result, patients were pre-assessed, either face-to-face or following telephone consultation, by a bowel screening endoscopy nurse and then referred on for colonoscopy if this was deemed suitable. If colonoscopy was unsuccessful then further bowel imaging by barium enema or CT pneumocolonography was attempted. As screening is biennial, two years worth of screening invitations was taken to comprise one complete screening round.

Participant details were obtained from a prospectively maintained database held by the Public Health Screening Unit in NHS Greater Glasgow and Clyde. Data on endoscopic findings and pathological diagnosis was obtained retrospectively from clinical information systems. These results formed the basis of our analysis.

Patients with a pathological diagnosis of adenomatous polyp were classified as being of low, intermediate or high risk of subsequent development of colorectal cancer in accordance with the British Society of Gastroenterology (BSG) guidelines (Cairns, Scholefield et al. 2010) (low risk; 1 to 2 polyps <1cm: intermediate risk; 3-4 polyps <1cm or $\geq$ 1 polyp $\geq$ 1cm: high risk; $\geq$5 polyps or $\geq$ 3 polyps of which $\geq$ 1 is $\geq$ 1cm).

In order to allow comparison between the results of a full colonoscopy screening programme with definitive colonic visualisation, and the potential results of a 'flexible sigmoidoscopy-first' protocol, a theoretical flexible sigmoidoscopy was calculated. All pathology up to and including the splenic flexure was deemed detectable by flexible

sigmoidoscopy. In those patients with pathology up to and including the splenic flexure, the results of potential adherence to the UK Flexible Sigmoidoscopy Trial protocol were considered. The indications for subsequent full colonoscopy, as per the UK Flexible Sigmoidoscopy trial (Atkin, Edwards et al. 2010), were ≥ 3 polyps; 1 polyp ≥ 1cm; presence of high grade dysplasia; villous or tubulovillous polyp histology.

The study was approved by the Public Health Directorate, NHS Greater Glasgow & Clyde as a review of current practice. No formal ethical approval was required.

Statistical analysis

Associations between categorical variables were examined using χ^2 tests for linear trend unless otherwise specified. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA). The positive predictive value (PPV) of detecting cancer was defined as the number of patients in whom a cancer was detected divided by the number of patients undergoing endoscopy. The PPV of neoplasia was defined as the number of patients in whom a cancer or adenomatous polyp was identified divided by the number of patients undergoing endoscopy and the PPV of significant neoplasia was the number of patients with either a cancer or, intermediate or high risk polyps divided by the number of patients undergoing endoscopy.

4.3 Results

From April 2009 to March 2011 inclusive, of 395 097 individuals invited to participate in screening, 204 461 (52%) responded of whom 6 085 (3%) tested positive. Of the 6085 positive tests, 1200 (20%) were strongly gFOBt positive, 4083 (67%) were FIT positive following a weakly positive gFOBt and 802 (13%) were FIT positive following an expired, incomplete or spoiled gFOBt kit. Of the 6 085 positive results, 4 631 (76%) attended for colonoscopy. Full results were available for 4 223 (91%) patients which formed the basis of our analysis.

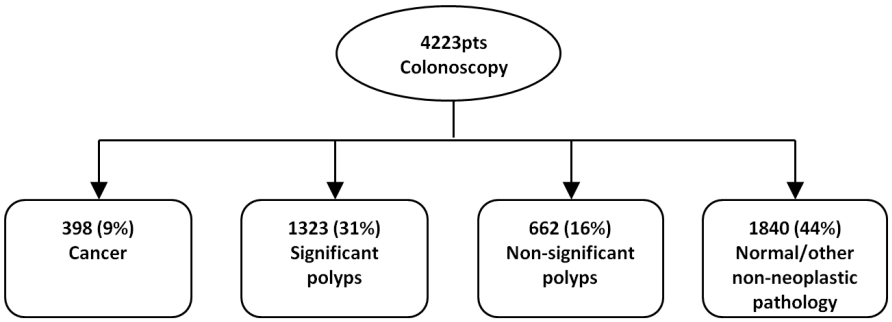
Outcomes of colonoscopy

Of the 4 223 in whom complete results were available, cancer was detected in 398 (9%) and adenomatous polyps in 1 985 (47%) (Figure 4.1a). Of those with adenomatous polyps, 1 323 (67%) were classified as intermediate or high risk polyps as per BSG guidelines, and therefore would have required further surveillance at 1 yearly or 3 yearly intervals. Overall there was a PPV for cancer of 9%, a PPV for significant neoplasia of 40%, and a PPV for all neoplasia of 56%.

Outcome from flexible sigmoidoscopy

Of the 4 223 in whom complete results were available, if a flexible sigmoidoscopy alone had been performed instead of a colonoscopy then cancer would have been detected in 307 (7%) and adenomatous polyps in 1 662 (39%) including high or intermediate risk in 1 152 (69%) (Figure 4.1b). Overall a PPV for cancer of 7%, a PPV for significant neoplasia of 35% and a PPV for all neoplasia of 47% would have been seen.

(a)



(b)

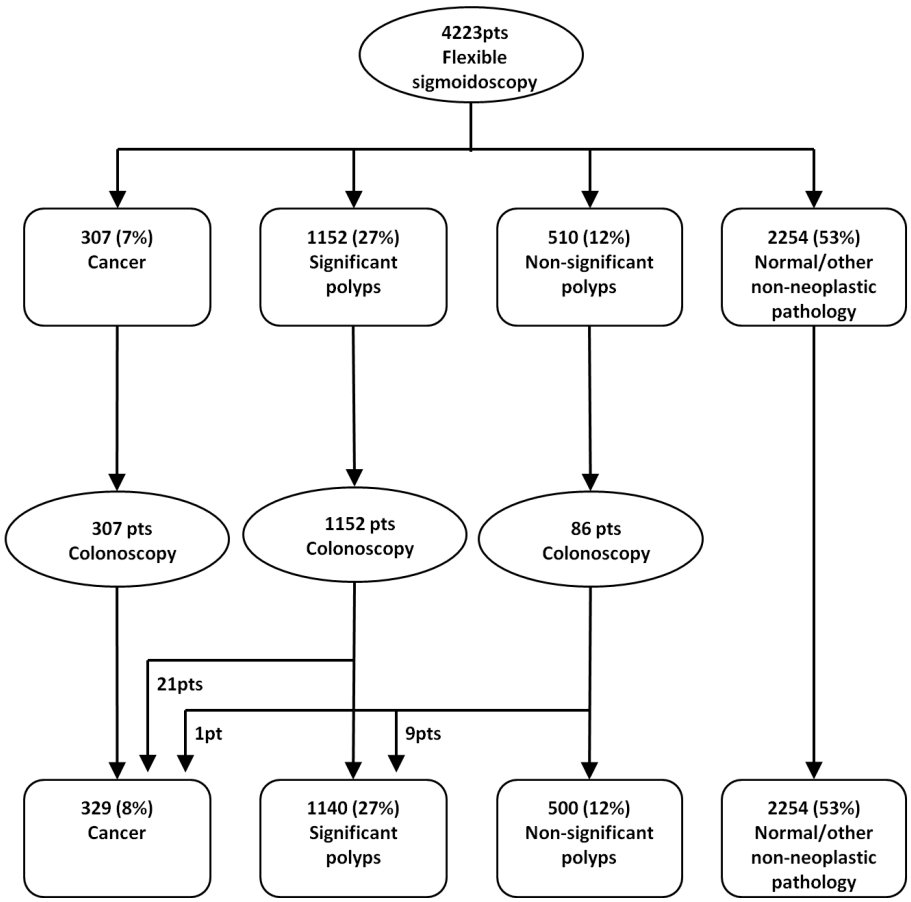


Figure 4.1: Outcome of colonoscopy (a) and theoretical outcomes of flexible sigmoidoscopy-first model (b)

Outcome using flexible sigmoidoscopy-first protocol

If the 'flexible sigmoidoscopy-first' protocol had been utilised then 1 546 (37%) of the 4 223 undergoing flexible sigmoidoscopy would have proceeded to a full colonoscopy (Figure 4.1b). Following this two stage process it can be calculated that a further 22 cancers would have been detected, resulting in 329 cancers that would have been diagnosed overall. Therefore, it can be calculated that 69 (17%) cases of cancer would have been missed with the 'flexible sigmoidoscopy-first' compared with the colonoscopy protocol. No further patients would have had a new diagnosis of adenomatous polyps, but of the 510 patients with low risk polyps seen on flexible sigmoidoscopy, 86 would have undergone a subsequent colonoscopy and nine would have an increased risk of polyps warranting further surveillance colonoscopy in due course. Overall, using the 'flexible sigmoidoscopy-first' model a PPV for cancer of 8%, a PPV for significant neoplasia of 35% and a PPV for all neoplasia of 47% would have been seen (Table 4.1).

Comparing the cancers detected through colonoscopy with the 'flexible sigmoidoscopy-first model' (Table 4.2) there were no differences in the age, sex or overall Dukes stage. The flexible sigmoidoscopy-first model detected fewer right sided cancers (7% vs 23%, $p<0.001$) and tumours were of an earlier T-stage ($p=0.049$).

Adjustment for type of positive test

The data were further stratified into three groups to adjust for the type of positive test that prompted referral for colonoscopy (strong gFOBt positive (gFOBt), FIT positive following a weak gFOBt (gFOBt/FIT) and FIT following an expired, incomplete or spoiled gFOBt kit (FIT)) (Table 4.3). The PPV for cancer, significant neoplasia and neoplasia at colonoscopy were highest in the gFOBt group (18%, 48% ,60% respectively) and lowest in the FIT group (4%, 27%, 45% respectively). Comparing the colonoscopy and 'flexible

sigmoidoscopy-first' model, the difference in the PPV for significant neoplasia and neoplasia remained significant across all three types of positive test. However, the difference in the PPV for cancer remained significant in the gFOBt group only (Table 4.3).

4.4 Discussion

The results of the present study confirm that a flexible sigmoidoscopy-first protocol would reduce detection of neoplasia within the context of a gFOBt/FIT bowel screening programme. Of the 398 cancers identified at colonoscopy, 329 (83%) would have been identified using the flexible sigmoidoscopy-first model compared with the current practice of colonoscopy. There was a relatively small reduction in the positive predictive value for detecting cancer, but there was a much larger reduction in the significant neoplasia and overall neoplasia rates. It was of particular interest that 1 546 (37%) patients would require a further procedure and only 31 (2%) of these would have had subsequent cancer or significant neoplasia detected as a result of the second procedure.

In the present study the overall results from the first screening round were similar to that from other regions with regards uptake, positivity and outcome following colonoscopy (Steele, McClements et al. 2009; Logan, Patnick et al. 2012). In particular, the fact that 46% of tumours detected through the screening programme were TNM Stage I tumours is in keeping with other studies confirming that large numbers of early stage tumours can be detected through the use of gFOBt (Steele, McClements et al. 2009). However, as with other studies, there was increased detection of left sided lesions, with 77% of tumours detected at colonoscopy in our series being distal to the splenic flexure (Morris, Whitehouse et al. 2012; Roxburgh, McTaggart et al. 2013; Steele, McClements et al. 2012). This disparity may be due to gut transit. The gFOBt tests for the peroxidase activity of haematin in faeces and so when haemoglobin is released by right sided tumours it can be degraded as it passes through the remainder of the large bowel, thereby leading to a false negative result (Morris, Whitehouse et al. 2012). The majority of patients who tested positive in the present study did so following a weak positive gFOBt and subsequent positive FIT, however, this will not have altered the false negative rate caused by the initial gFOBt. The higher proportion of left sided lesions detected by gFOBt is likely positively to

bias the results for the diagnostic yield of flexible sigmoidoscopy versus colonoscopy. As a result, it is possible that an even greater number of cancers would not be detected if other less discriminatory baseline screening tools had been employed such as the FIT.

The sub analysis performed in the present study to explore the difference between gFOBt, gFOBt/FIT and FIT was of interest as the SBoSP differs from the current gFOBt screening programme used in England, in that a 'positive test' actually represents the outcome from three separate possible screening mechanisms each with their own test characteristics of sensitivity and specificity (Fraser, Digby et al. 2012). The present study found the difference in the PPV of cancer between colonoscopy and a flexible sigmoidoscopy-first model was significant only in the gFOBt group and not in the gFOBt/FIT or FIT group. This is likely to be due to the lower overall PPV for cancer in both the latter groups, a finding that has been reported previously (Fraser, Digby et al. 2012).

Although there were no differences seen in the patient demographics of those having cancer detected via colonoscopy or theoretically via the flexible sigmoidoscopy-first model, tumours were of a more advanced T-stage in the colonoscopy group. This is likely due to the fact that right sided tumours detected through screening are larger than left sided tumours. Use of a flexible sigmoidoscopy-first protocol may increase the number of early stage left sided lesions while allowing right sided lesions to grow undetected. Small right sided tumours may not bleed to the extent that larger tumours do and as a result there may be a higher threshold for tumour size before gFOBt assessment reliably detects these cancers.

Therefore, it may be that the recent decision to combine the current biennial gFOBt with an additional once off flexible sigmoidoscopy in England may also result in a disproportionate increase in the number of left-sided lesions detected. A potential solution to this problem of detection may lie with the use of FIT as a primary screening tool as a recent study has

shown that FIT may be equally as sensitive at detecting proximal and distal colonic lesions (de Wijkerslooth, Stoop et al. 2012). FIT specifically targets human haemoglobin and, rather than the binary response that the gFOBt produces, it can be quantitative. This can allow thresholds to be determined based on relative sensitivity and specificity of the test for a given population. Moreover, there is evidence that the FIT may also increase participation (Hol, van Leerdam et al. 2010). The present study had lower PPVs for cancer, neoplasia and significant neoplasia in the FIT group than the gFOBt group. This may be related to the current low analytical detection limit that the FIT test uses compared with gFOBt (10µg Hb/g faeces for the FIT compared with 600µg Hb/g faeces for the gFOBt). Were FIT to be used as a primary screening tool this detection limit can be adjusted accordingly.

One further aspect that should be considered in this analysis is the cost of a two stage diagnostic test following a positive gFOBt/FIT to the NHS. Although the present study was not designed to perform a full economic analysis of the current screening pathway and the proposed flexible sigmoidoscopy-first model, figures from a recent study (Whyte, Chilcott et al. 2012) estimate the average cost of a flexible sigmoidoscopy (+/- polypectomy) to be £191 and the average cost of a colonoscopy (+/- polypectomy) to be £221. A simple costing based on these figures and the results from the present study would estimate the overall cost of performing diagnostic tests to be around £933 200 for the colonoscopy group and that the overall cost of performing diagnostic tests if a flexible sigmoidoscopy-first model had been used, to be around £1 146 100. This represents a 20% increase in cost over the use of single diagnostic colonoscopy. Moreover, given the additional costs of a two stage diagnostic test this estimate is likely to be conservative. In order to carry out a more detailed cost analysis further details of the flexible sigmoidoscopy-first model would need to be estimated. These would include the number of procedures performed on a given day, the duration of the procedure, use of sedation and

choice of bowel preparation. Additionally, there would also be substantial additional cost implications for the patients themselves, if a two stage diagnostic test were to be employed. This information was not available in the present analysis.

An additional factor when discussing the use of flexible sigmoidoscopy within a screening setting is that of quality control. The SBoSP currently records caecal intubation rate (QIS 2007) as its mainstay of endoscopic quality control as a clear end point for colonoscopy with rates above 90% as a minimum standard. The bowel screening programme in England (BCSP 2011) has additional auditable control measures such as cancer detection rate, adenoma detection rate and colonoscope withdrawal time for negative colonoscopies. There are currently no such national standards for flexible sigmoidoscopy. For example, there is no clear end-point to the examination. In the UK flexible sigmoidoscopy trial (Atkin, Cook et al. 2002) the endoscope was inserted as far as could be achieved without causing undue pain or distress which was usually the junction of the sigmoid and descending colon. The Italian flexible sigmoidoscopy trial (Segnan, Armaroli et al. 2011) aimed beyond this point, and one of the key factors for an adequate flexible sigmoidoscopy in the PLCO trial (Weissfeld, Schoen et al. 2005) was passing the endoscope beyond 50cm. Clearly, these definitions differ and the use of the splenic flexure as the cut-off point in the present study is theoretical. Hence, the differences in neoplasia rates between the colonoscopy and flexible sigmoidoscopy-first model may be underestimated in the present study.

The present study has not considered adverse events. In a recent analysis of the Bowel Cancer Screening Programme in England, of the 18 135 colonoscopies performed 17 (0.09%) colonic perforations and 42 (0.2%) episodes of post procedure per rectum bleeding were noted (Logan, Patnick et al. 2012). This rate is higher than the findings of the UK Flexible Sigmoidoscopy Trial where, following 40 332 flexible sigmoidoscopies

only 1 (0.002%) perforation occurred and 77 (0.2%) episodes of post procedure rectal bleeding were noted (Atkin, Cook et al. 2002). A rudimentary calculation based on these figures would estimate that 4 (4223 x 0.09%) perforations and 8 (4223 x 0.2%) episodes of bleeding would be expected in our population following colonoscopy and that 1 (4223 x 0.002% + 1546 x 0.09%) perforation and 11 (4223 x 0.2% + 1546 x 0.2%) episodes of bleeding would be expected if a flexible sigmoidoscopy-first protocol had been used. It is of interest, therefore, that complication rates may be similar in these two approaches, although it is important to note that there may be confounding factors not included in this simple analysis.

This study has limitations in that it is based on a theoretical model and does not entirely represent what would be seen in the real world. For example, the uptake of colonoscopy following a positive test in this study was 76%, either due to the patient declining the test or not being medically fit to take part. It might be that the uptake would have been higher had flexible sigmoidoscopy been offered instead. However, performing a randomised controlled trial to obviate such bias is no longer feasible.

In summary the results of the present chapter indicate that, despite evidence that a high proportion of test positive patients have left sided colonic pathology, the use of flexible sigmoidoscopy as a primary diagnostic tool would not detect a substantial proportion of both cancers and adenomatous polyps. Furthermore, it would also subject a significant proportion of patients to two procedures with considerable implications for patient and cost.

Table 4.1: Comparison of neoplasia detection rates at endoscopy

	Colonoscopy	Flexible sigmoidoscopy-first	p-value
	n (%)	n (%)	
All patients	4223 (100)	4223 (100)	
Cancer	398 (9)	329 (8)	0.007
Significant neoplasia	1721 (40)	1469 (35)	<0.001
Neoplasia	2383 (56)	1969 (47)	<0.001

Table 4.2: All patients diagnosed with cancer: colonoscopy vs flexible sigmoidoscopy-first model

	Colonoscopy n (%)	Flexible sigmoidoscopy-first model n (%)	p-value
	398 (100%)	329 (100%)	
Age (years)			
≤55	47 (12%)	42 (13%)	
56-64	106 (27%)	94 (29%)	
≥ 65	245 (62%)	193 (59%)	0.463
Sex			
Male	265 (67%)	227 (69%)	
Female	133 (34%)	102 (31%)	0.489
Site			
Rectal	113 (28%)	113 (34%)	
Left sided	193 (49%)	193 (58%)	
Right sided	92 (23%)	23 (7%)	<0.001
TNM Stage[a]			
I	182 (46%)	170 (47%)	
II	81 (20%)	55 (17%)	
III	95 (23%)	70 (21%)	
IV	26 (7%)	23 (7%)	0.348
T-stage[b]			
1	144 (39%)	138 (45%)	
2	58 (16%)	51 (17%)	
3	141 (38%)	101 (33%)	
4	27 (7%)	16 (5%)	0.049
N-stage[b]			
0	269 (73%)	231 (76%)	
1	67 (18%)	54 (18%)	
2	34 (9%)	21 (7%)	0.288

[a]Patients with full staging details (n=384 colonoscopy, n=318 flexible sigmoidoscopy-first)
[b]Patients who underwent resection (n=370 colonoscopy, n=306 flexible sigmoidoscopy-first)

Table 4.3: Comparison of neoplasia detection rates at endoscopy adjusted for type of positive test

	Colonoscopy n (%)	Flexible sigmoidoscopy-first model n (%)	p-value
gFOBt	747 (100)	747 (100)	
Cancer	132 (18)	102 (14)	0.033
Significant neoplasia	359 (48)	311 (42)	0.013
Neoplasia	450 (60)	372 (50)	<0.001
gFOBt/FIT	2995 (100)	2995 (100)	
Cancer	245 (8)	212 (7)	0.108
Significant neoplasia	1234 (41)	1056 (35)	<0.001
Neoplasia	1719 (57)	1433 (48)	<0.001
FIT	481 (100)	481 (100)	
Cancer	21 (4)	15 (3)	0.308
Significant neoplasia	128 (27)	102 (21)	0.049
Neoplasia	214 (45)	164 (34)	0.001

5 THE IMPACT OF ASPIRIN, STATIN AND ACE-INHIBITOR USE ON THE LIKELIHOOD OF SIGNIFICANT NEOPLASIA IN PATIENTS UNDERGOING COLONOSCOPY FOLLOWING A POSITIVE SCREENING TEST

5.1 Introduction

While screening may improve outcomes through the detection of early stage disease, not all tumours are detected through the programme in its current format. Therefore there is substantial ongoing interest in the field of chemoprevention, with the use of certain drugs to reduce an individual's risk of cancer. For example, there is considerable evidence that aspirin may reduce an individual's likelihood of developing both pre-cancerous adenomata (Baron, Cole et al. 2003; Benamouzig, Deyra et al. 2003; Sandler, Halabi et al. 2003; Cole, Logan et al. 2009) and colorectal cancer (Thun, Namboodiri et al. 1991; Flossmann and Rothwell 2007). Moreover, it may have an impact on reducing cancer deaths in those with colorectal tumours (Rothwell, Wilson et al. 2010; Rothwell, Fowkes et al. 2011). The precise mechanism for aspirin's effect is not entirely clear but appears to be due to both its role in modulating the inflammatory response and also through more complex direct effects on tumour cells themselves (Chan, Arber et al. 2012).

In addition, statins have also been suggested to reduce an individual's risk of developing both colorectal cancer and advanced adenomas. The evidence for this has been variable in individual trials (Poynter, Gruber et al. 2005; Jacobs, Kodach et al. 2011; Simon, Rosenberg et al. 2012), however a recent meta-analysis involving 11 randomised control trials, 13 case-control studies and 8 cohort studies concluded that chronic statin usage did indeed have a small protective impact on colorectal cancer occurrence (Bardou, Barkun et al. 2010). The mechanism for its effect is thought to arise through a combination of

increased induction of tumour cell apoptosis, inhibition of cell growth or angiogenesis, or through enhancement of the immune response (Gauthaman, Fong et al. 2009).

Furthermore, some evidence has emerged that angiotensin converting enzyme inhibitors (ACE-i) may also have a chemopreventative effect (Lever, Hole et al. 1998), and in particular for colonic cancer their use may reduce the development of pre-cancerous adenomata (Kedika, Patel et al. 2011). This may be due to a role of angiotensin converting enzyme in influencing local tumour growth and neoangiogenesis (Rocken, Neumann et al. 2007).

However, each of these drugs each has their own side-effect profile. This may be magnified when used in high doses, and so far no single agent has been recommended for chemopreventive use in the general population. Use of these drugs for chemoprevention in combination has previously been suggested (Zhou, Cheng et al. 2012) but not studied in a population setting, however, the concept of a 'polypill' to reduce cardiovascular risk has previously been proposed (Wald and Law 2003; Rodgers, Patel et al. 2011).

The aim of the present study was to assess the affect of aspirin, statins and ACE-inhibitors both in isolation and in combination, on an individual's risk of neoplasia in patients who tested positive in a colorectal cancer screening programme and subsequently underwent colonoscopy.

5.2 Materials and methods

Beginning in April 2009 all males and females between the age of 50 and 74 and registered with a GP in NHS Greater Glasgow & Clyde (NHS GG&C) were identified via their Community Health Index (CHI) and invited to participate in the Scottish Bowel Screening Programme (SBoSP). Participants were sent a gFOBt kit and asked to provide 2 samples from 3 separate faecal specimens. In the case of weakly positive or spoiled kits participants were sent a FIT kit. Analysis and processing of the gFOBt/FIT kits in the SBoSP has been described previously in Chapter 1. Following a positive result, patients were pre-assessed, either face-to-face or following telephone consultation, by a bowel screening endoscopy nurse and then referred on for colonoscopy if this was deemed suitable. Details on patient medications were automatically uploaded to the Bowel Screening IT system from the Scottish Care Information (SCI) Gateway system which provides an interface between primary and secondary care records. This allows for details of patients regular medication, as held by their General Practitioner to be obtained. As part of the pre-assessment interview patient medications were checked with this electronic record. A user of medication was defined as an individual who had either aspirin, statin or ACE-i usage at time of pre-assessment documented as per this method. Patient details were obtained from the prospectively maintained Bowel Screening IT system managed by the Public Health Screening Unit at NHS GG&C.

Data on endoscopic findings and pathological diagnosis was obtained retrospectively from clinical information systems. The presence of any colorectal pathology that could account for a positive stool test was noted. This included, but was not limited to colorectal cancer, dysplastic polyps, and non-neoplastic colorectal pathology such as colitis or haemorrhoids. The presence of uncomplicated diverticulosis and hyperplastic polyps were noted as normal findings.

In those patients in whom a pathological diagnosis of dysplastic polyps was reached, they were classified as being of a low risk, intermediate risk or high risk of subsequent development of colorectal cancer as per British Society of Gastroenterology (BSG) guidelines (Atkin and Saunders 2002) (low risk; 1 to 2 polyps <1cm: intermediate risk; 3-4 polyps <1cm or $\geq$ 1 polyp $\geq$ 1cm: high risk; $\geq$5 polyps or $\geq$ 3 polyps of which $\geq$ 1 is $\geq$ 1cm). Advanced neoplasia was defined as patients with either colorectal cancer or dysplastic polyps classified as intermediate or high risk as per BSG guidelines.

Deprivation category was calculated using the Scottish Index of Multiple Deprivation (SIMD) which is an index of relative deprivation combining 38 indicators across 7 domains, namely: income, employment, health, education, skills and training, housing, geographic access and crime. The overall index is a weighted rank for each domain allowing postcodes to be ranked in order of deprivation across Scotland. Quintiles of deprivation were used to assign patients a relative deprivation category based on their postcode at time of colonoscopy with the first quintile representing the most deprived and the fifth quintile, the least deprived (SIMD 2009).

Permission for the study was granted by the Caldicott Guardian of the data, and data was stored and analysed in an anonymised manner.

Statistical analysis

Associations between categorical variables were examined using χ^2 tests for linear trend unless otherwise specified. Both univariate and multivariate logistical regression was used to calculate odds ratios. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA)

5.3 Results

From April 2009 to March 2011 representing the first complete round of screening in NHS GG&C, 395 096 individuals were invited to participate, 204 461 (52%) responded and 6 085 (3.0%) tested positive. Of those who tested positive, 4 631 (76%) patients proceeded to undergo colonoscopy. Complete results on both outcomes following colonoscopy and medications noted at pre-assessment were available for 4 188 (90%) patients which formed the basis of our analysis. The majority of positive results were due to a positive FIT (3449 (82%) patients).

Presence of colorectal pathology

Of the 4 188 patients in whom complete results were available, colorectal pathology was identified in 3 043 (73%) patients (Figure 5.1). Patients with colorectal pathology were more likely to be older ($p<0.001$), male ($p<0.001$), less deprived ($p<0.05$) and have tested positive through the gFOBt route ($p<0.05$) than those without any (Table 5.1). In contrast, those that were on aspirin were less likely to have colorectal pathology identified at colonoscopy ($p<0.05$). There were no associations between statin or ACE-i usage and the presence of colorectal pathology. On multivariate analysis, older age and male sex was remained associated with increased risk of colorectal pathology (both $p<0.001$) and aspirin usage remained associated with a reduced risk of colorectal pathology ($p<0.001$).

Presence of advanced neoplasia

Of the 3 043 patients with colorectal pathology, advanced neoplasia was identified in 1 704 (56%) patients (Figure 5.1). Patients with advanced neoplasia were more likely to be older, male, less deprived and have tested positive through gFOBt route (all $p<0.001$) than those without (Table 5.2). In contrast, those on aspirin ($p<0.001$), statins ($p<0.001$) or ACE-i ($p<0.05$) were all less likely to have advanced neoplasia at colonoscopy. As the majority of

patients on at least one of these medications were in fact on multiple medications for the purposes of multivariate analysis the variable ≥1 medication was entered into the model. The associations identified on univariate analysis persisted in the multivariate model. The risk of advanced neoplasia was also then examined in medication combinations (Table 5.3). Similar odds ratios were seen between combinations of these three medications (OR 0.64; 95% CI 0.50-0.83 to 0.71; 95% CI 0.57-0.89) where the risk of non-significant pathology was taken as the reference. Odds ratios for those on ≥1 medication (OR 0.67; 95% CI 0.56-0.78) or ≥2 medications (OR 0.67; 95% CI 0.55 – 0.81) were also similar.

Presence of cancer

Of the 1 704 patients with advanced neoplasia, colorectal cancer was identified in 392 (23%) patients (Figure 5.1). Patients with cancer were more likely to be older ($p=0.001$), male ($p<0.05$) and have tested positive through the gFOBt route ($p<0.001$) than those with advanced adenomas only (Table 5.4). These associations remained significant on multivariate analysis. There was a non-significant trend to those with cancer identified being less likely to be on a statin ($p=0.071$).

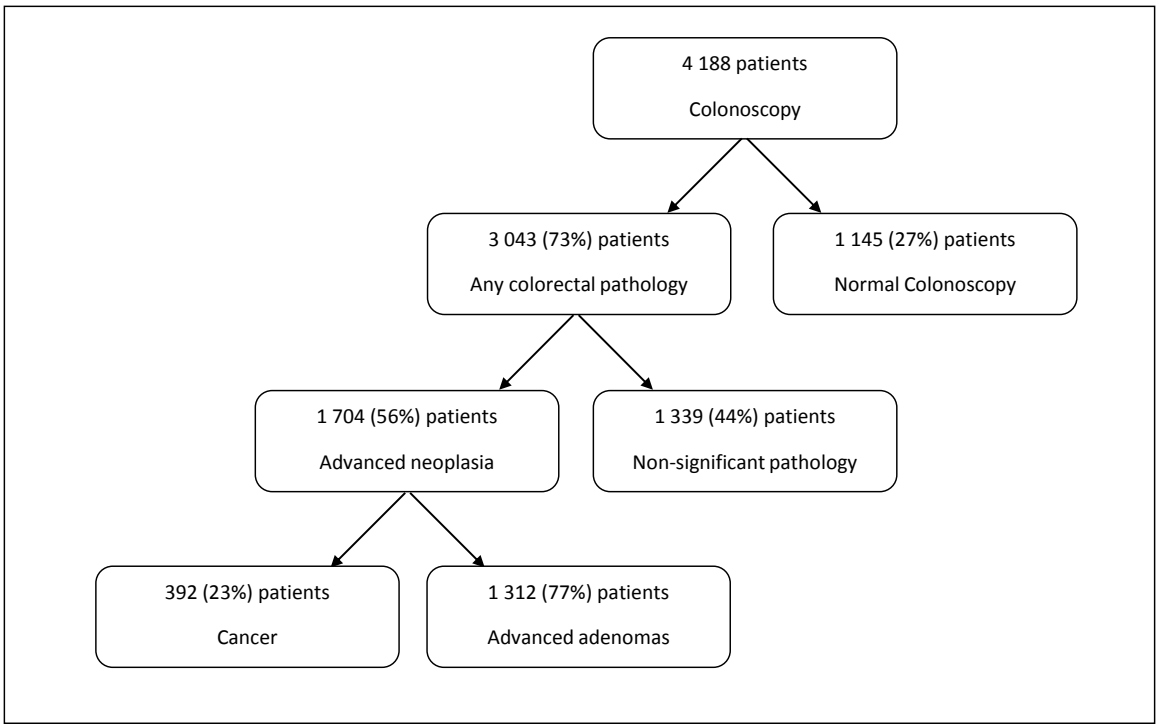


Figure 5.1: Outcomes from colonoscopy following a positive screening test

5.4 Discussion

The results of the present study report for the first time, a reduced incidence of advanced neoplasia in patients who are on a statin or an ACE-i that undergo colonoscopy following a positive stool test within a population based colorectal cancer screening programme. In addition, it confirms previous work that has shown a reduced incidence of advanced neoplasia in those on aspirin. Overall, the results suggest that there may be role for population based usage of these medications in reducing the incidence of colorectal neoplasia.

The reduction in incidence of advanced neoplasia of 33% in those on at least one medication is similar to the 28% reduction seen in a recent meta-analysis of the effect of aspirin in preventing advanced lesions in a non-screened population (Cole, Logan et al. 2009). Studies have also previously shown a lower yield of neoplasia in those on aspirin who undergo a colonoscopy following a positive gFOBt (Clarke, Jack et al. 2006; Sawhney, McDougall et al. 2010; Lee, Hull et al. 2012). However, previous work has been unable to adjust for the false positive effect of aspirin that can occur with gFOBt tests, and therefore were unable to definitively attribute this to a chemopreventative effect. For example, there is evidence that aspirin can increase gFOBt false positives due to its antiplatelet activity causing occult bleeding in an otherwise normal gastrointestinal tract. In the present study, by removing all those in whom no cause for the positive stool test was found, the impact of this confounding factor was minimised. Furthermore, the majority of our patients tested weakly positive on gFOBt and actually proceeded to colonoscopy only following a confirmatory positive FIT. Indeed, previous authors have reported a limited effect of aspirin usage on FIT specificity (Levi, Rozen et al. 2009; Brenner, Tao et al. 2010).

In addition, the reduced incidence of advanced neoplasia that was seen in the present study was seen not only in aspirin but in statins and ACE-i that have not previously been reported to cause false positive stool tests. The present study supports this assumption as aspirin but neither statins nor ACE-i usage was associated with a higher likelihood of having a normal colonoscopy.

The stage at which these medications might impact on the adenoma-carcinoma sequence has been previously speculated (Rocken, Neumann et al. 2007; Gauthaman, Fong et al. 2009; Chan, Arber et al. 2012). Of interest, in the present study there was no significant impact of medications on the presence of cancer within those with advanced neoplasia. Therefore, it may indicate that rather than affecting cancer progression and growth, these medications exert their influence earlier in the adenoma-carcinoma pathway by preventing adenoma development.

From previous in vivo and in vitro studies there is not only debate as to which stage of the adenoma-carcinoma sequence is affected by both aspirin, statins, and ACE-i but also the precise mechanism of action. For example, with aspirin, there is evidence for both a direct local effect on tumour cells and the tumour micro-environment, and a systemic effect of the drug on circulating inflammatory cytokines (Chan, Arber et al. 2012). The clinical limitations with many in-vitro studies are that large concentrations of aspirin are required to create a local effect. Whilst not specifically noted, it is likely that the vast majority of patients in the present study were taking low doses designed for cardiac prevention and therefore the local effects on colonic mucosa were likely to be limited. This favours the premise that the reduction in neoplasia seen in the present study is mediated through a systemic effect. If this was proven to be the case then the reduction in neoplasia risk detected by the present study is likely to be an underestimation due to the non-discriminatory use of these medications. There is evidence that an elevated host systemic

inflammatory response is associated with the presence of cancer (Proctor, Talwar et al. 2010) and hence it may be that more targeted therapy to those at risk of neoplasia (e.g. with an elevated systemic inflammatory response) may yield a greater benefit. It would be of interest to examine medication usage, neoplasia risk and markers of the systemic inflammatory response within population studies and further work is warranted.

It is important to note that conclusions drawn from the present study may not necessarily be representative of the population as a whole who were invited to screening. Only 52% of patients responded to the screening invite and just over three quarters of those who tested positive actually underwent colonoscopy. In Chapter 3, it has been reported that those who fail to respond to screening are more likely to be male, younger and more socio-economically deprived and that those who fail to progress to colonoscopy following a positive test are more likely to be deprived. Further work exploring medication usage and subsequent development of neoplasia in those who choose not to participate in screening is required.

A limitation of the present study is that data on dosage, duration or compliance with use of these medications was not collected. Therefore, we were not able to draw conclusions on favoured dosing for chemoprevention, nor were we able to separate those who had taken these medications for a period of weeks from those that had been on them for several years. Furthermore, a potential concern of the present cross-sectional study design is that the medication recorded does not reflect ongoing exposure. Nevertheless, given that the recorded medications are used to treat existing co-morbid disease it is likely that such medication would be taken on an ongoing basis. In addition, the majority of patients who were on at least one of these medications were in fact on several of them. Therefore, performing multivariate analysis to assess which was of most importance with this large degree of multicollinearity was not meaningful and the effect of an individual medication

could not be reliably estimated. However, this represents a real-life population setting where the majority of patients are likely to be on a combination of medications. Analysis of the risk of neoplasia and the association with medication usage, stratified for location within the colon was also not performed. Previous studies have found the greatest risk reduction with aspirin usage and with lesions of the proximal colon (Rothwell, Fowkes et al. 2011) and hence examining this in our population may have been of interest. However, there is an inherent problem with using data derived from occult blood stool based colorectal cancer screening programmes for this, as such screening tests are less sensitive for right sided lesions (Logan, Patnick et al. 2012). This altered sensitivity creates a skewed study population undergoing colonoscopy where lesions are mainly on the left side of the colon. For example only 17% of those with significant neoplasia in our study population had isolated right sided lesions (data not presented). Such sample bias would negate any meaningful conclusions being drawn from subanalysis based on the location of neoplastic lesions and so such an analysis was not undertaken. Also, while consideration was made to adjust for age, sex and socioeconomic deprivation, there are other potential confounding factors such as a significant family history or previous history of colonic neoplasia that have not been included in the present analysis. In particular, there is now robust evidence that patients with hereditary non-polyposis colorectal cancer (HNPCC) or familial adenomatous polyposis (FAP) may derive substantial benefit from aspirin chemoprophylaxis (Burn, Bishop et al. 2011; Burn, Gerdes et al. 2011). However, the overall incidence of these hereditary cancers in our study population is likely to be small (<10%).

In conclusion, the present chapter reports that there is a reduced incidence of advanced colorectal neoplasia in patients who are on aspirin, statins or ACE-i undergoing colonoscopy following a positive stool test within a population based screening programme. This effect persists when adjustment is made for the possible false positivity

effect of aspirin on gFOBt testing, suggesting that this reduction may be due to a chemopreventative mechanism. Overall, this supports the theory that population based usage of these medications in this age group may reduce the incidence of colorectal neoplasia. Further work is required to explore not only this concept but the perceived association with the host systemic inflammatory response, within the context of a national bowel screening programme.

Table 5.1: Study population and likelihood of detecting any colorectal pathology at colonoscopy following a positive stool test

	All pts n (%)	Colorectal pathology n (%)	Normal colonoscopy n (%)	p-value	Risk of colorectal pathology (multivariate analysis) O.R. (95% C.I.)	p-value
	4188	3043	1145			
Age						
≤55	877 (21)	565 (19)	312 (27)		1	
56-64	1280 (31)	925 (30)	355 (31)		1.41 (1.17 – 1.71)	<0.001
≥ 65	2031 (49)	1553 (51)	478 (42)	<0.001	1.89 (1.58 – 2.27)	<0.001
Sex						
Female	1699 (41)	1053 (35)	646 (56)		1	
Male	2489 (59)	1990 (65)	499 (44)	<0.001	2.49 (2.16 – 2.86)	<0.001
Deprivation category						
1 (most deprived)	1506 (36)	1060 (35)	446 (39)		1	
2	785 (19)	568 (19)	217 (19)		1.08 (0.88 – 1.31)	0.461
3	666 (16)	507 (17)	159 (14)		1.30 (1.05 – 1.61)	0.017
4	527 (13)	380 (13)	147 (13)		1.02 (0.81 – 1.28)	0.879
5 (least deprived)	699 (17)	525 (17)	174 (15)	0.017	1.21 (0.98 – 1.49)	0.080
Type of positive stool test						
FIT	3449 (82)	2482 (82)	967 (84)		1	
gFOBt	739 (18)	561 (18)	178 (16)	0.029	1.20 (0.99 – 1.45)	0.062
Aspirin						
No	3531 (84)	2592 (85)	939 (82)		1	
Yes	657 (16)	451 (15)	206 (18)	0.012	0.67 (0.55 – 0.81)	<0.001
Statin					-	
No	3308 (79)	2422 (80)	886 (77)			
Yes	880 (21)	621 (20)	259 (23)	0.117		
ACE-i					-	
No	3682 (88)	2672 (88)	1010 (88)			
Yes	506(12)	371 (12)	135 (12)	0.722		
≥1 medications					-	
No	3088 (74)	2271 (75)	817 (71)			
Yes	1100 (26)	772 (25)	328 (29)	0.032		

Table 5.2: Risk of advanced-neoplasia in those with colorectal pathology at colonoscopy

	All pts n (%)	Advanced-neoplasia n (%)	Non-significant pathology n (%)	p-value	Risk of advanced-neoplasia (multivariate analysis) O.R. (95% C.I.)	p-value
	3043	1704	1339			
Age						
≤55	565 (19)	263 (15)	302 (23)		1	
56-64	925 (30)	513 (30)	412 (31)		1.48 (1.19 – 1.83)	<0.001
≥ 65	1553 (51)	928 (55)	625 (47)	<0.001	1.89 (1.55 – 2.31)	<0.001
Sex						
Female	1053 (35)	503 (30)	550 (41)		1	
Male	1990 (65)	1201 (70)	780 (59)	<0.001	1.70 (1.46 – 1.99)	<0.001
Deprivation category						
1 (most deprived)	1060 (35)	554 (33)	506 (38)		1	
2	568 (19)	324 (19)	244 (18)		1.16 (0.94 – 1.43)	0.160
3	507 (17)	278 (16)	228 (17)		1.05 (0.85 – 1.31)	0.653
4	380 (13)	232 (14)	148 (11)		1.33 (1.04 – 1.70)	0.021
5 (least deprived)	525 (17)	313 (18)	212 (16)	<0.001	1.29 (1.04 – 1.60)	0.021
Type of positive stool test						
FIT	2482 (82)	1351 (79)	1131 (84)		1	
gFOBt	561 (18)	353 (21)	208 (16)	<0.001	1.39 (1.14 – 1.68)	0.001
Aspirin					-	
No	2592 (85)	1488 (87)	1104 (82)			
Yes	451 (15)	216 (13)	235 (18)	<0.001		
Statin					-	
No	2422 (80)	1409 (83)	1013 (76)			
Yes	621 (20)	295 (17)	326 (24)	<0.001		
ACE-i					-	
No	2672 (88)	1524 (89)	1148 (86)			
Yes	371 (12)	180 (11)	191 (14)	0.002		
≥1 medications						
No	2271 (75)	1330 (78)	941 (70)		1	
Yes	772 (25)	374 (22)	398 (30)	<0.001	0.59 (0.50 – 0.70)	<0.001

Table 5.3: Combinations of medications and risk of advanced-neoplasia in those with colorectal pathology at colonoscopy

	Aspirin		**Statin**		**ACE-i**			**Aspirin & Statin**	
All pts n	451		621		371			371	
O.R. (95% C.I.)	0.68 (0.56-0.83)	p<0.001	0.65 (0.55-0.78)	p<0.001	0.71 (0.57-0.89)	p=0.002			
Aspirin n (%) No Yes			250 (40) 371 (60)		170 (46) 201 (54)				
O.R. (95% C.I.)			0.69 (0.56-0.86)	p=0.001	0.67 (0.51-0.90)	p=0.006			
Statin n (%) No Yes					93 (25) 278 (75)				
O.R. (95% C.I.)					0.64 (0.50-0.83)	p<0.001			
ACE-i n (%) No Yes								192 (52) 179 (48)	
O.R. (95% C.I.)								0.66 (0.49-0.90)	p=0.007

Reference category = non-significant pathology

Table 5.4: Risk of cancer in those with advanced-neoplasia at colonoscopy

	All pts n (%)	Cancer n (%)	Advanced adenoma n (%)	p-value	Risk of cancer (multivariate analysis) O.R. (95% C.I.)	p-value
	1704	392	1312			
Age						
≤55	263 (15)	46 (12)	217 (17)		1	
56-64	513 (30)	104 (27)	409 (31)		1.22 (0.82 – 1.80)	0.323
≥ 65	928 (55)	242 (62)	686 (52)	0.001	1.72 (1.20 – 2.45)	0.003
Sex						
Female	503 (30)	132 (34)	371 (28)		1	
Male	1201 (70)	260 (66)	941 (72)	0.040	0.75 (0.59 – 0.96)	0.023
Deprivation category					-	
1 (most deprived)	554 (33)	118 (30)	436 (33)			
2	324 (19)	66 (17)	258 (20)			
3	278 (16)	72 (19)	206 (16)			
4	232 (14)	63 (16)	169 (13)			
5 (least deprived)	313 (18)	71 (18)	242 (19)	0.184		
Type of positive stool test						
FIT	1351 (79)	264 (67)	1087 (83)		1	
gFOBt	353 (21)	128 (33)	225 (17)	<0.001	2.41 (1.87 – 3.12)	<0.001
Aspirin					-	
No	1488 (87)	349 (89)	1139 (87)			
Yes	216 (13)	43 (11)	173 (13)	0.247		
Statin					-	
No	1409 (83)	336 (86)	1073 (82)			
Yes	295 (17)	56 (14)	239 (18)	0.071		
ACE-i					-	
No	1524 (89)	353 (90)	1171 (89)			
Yes	180 (11)	39 (10)	141 (11)	0.652		
≥1 medications					-	
No	1330 (78)	318 (81)	1012 (77)			
Yes	374 (22)	74 (19)	300 (23)	0.094		

6 AN EXAMINATION OF THE RELATIONSHIP BETWEEN COLORECTAL SYMPTOMS AND OUTCOME AT COLONOSCOPY FOLLOWING A POSITIVE FAECAL OCCULT BLOOD TEST

6.1 Introduction

Currently, within the UK and indeed within the West of Scotland as discussed in Chapter 2, the majority of patients are diagnosed following symptomatic presentation. However, it is widely accepted that symptoms for bowel cancer can be multiple and non-specific. For example it has been previously reported that only 6% of patients referred to a surgical clinic with lower gastrointestinal (GI) symptoms will have colorectal cancer detected (Thompson, Perera et al. 2007). In addition, when individual symptoms are studied both in isolation and in combination they can only achieve positive predictive values for colorectal cancer of approximately 20% (Thompson, Perera et al. 2007)

Examination of data from the UK pilot studies of the bowel screening programmes have found that there is a high rate of lower GI symptoms in those who test positive and undergo colonoscopy, and has suggested that rather than pick up asymptomatic cancers, screening represents an additional way of symptomatic individuals to present (Ahmed, Leslie et al. 2005; Harmston, Akwei et al. 2010). Previous work however, has been limited by relatively small numbers and has failed to control for the confounding effect of non-neoplastic colorectal pathology detected at screening and potentially responsible for patient symptoms.

The aim of this study was to assess the prevalence of lower GI symptoms in patients who tested positive via the Scottish Bowel Screening Programme (SBoSP) in our geographical area and then subsequently underwent colonoscopy, and to correlate these with clinical outcomes.

6.2 Materials and methods

The Scottish Bowel Screening Programme (SBoSP) is a biennial occult blood screening programme and was introduced in NHS Greater Glasgow & Clyde in April 2009. Methodology data on the screening algorithm and processing of samples and has been described in Chapter 2. Prior to colonoscopy, individuals were pre-assessed, either face-to-face or following telephone consultation, by a bowel screening pre-assessment nurse. As part of the pre-assessment interview individuals were asked whether they had any bowel symptoms. Further details on the type and duration of symptoms were recorded as free text during this process. This prospectively collected data was then analysed retrospectively to assess for the presence of either rectal bleeding, a change in bowel habit, abdominal pain or tenesmus. Individuals with significant symptoms were defined as individuals with either one or more of these four specific symptoms.

Data on endoscopic findings and pathological diagnosis was obtained retrospectively from clinical information systems. The presence of uncomplicated diverticulosis and hyperplastic polyps were noted as normal findings. In those patients in whom a pathological diagnosis of dysplastic polyps was reached, they were classified as being of a low risk, intermediate risk or high risk of subsequent development of colorectal cancer as per BSG guidelines (Cairns, Scholefield et al. 2010) (low risk; 1 to 2 polyps <1cm: intermediate risk; 3-4 polyps <1cm or $\geq$ 1 polyp $\geq$ 1cm: high risk; $\geq$5 polyps or $\geq$ 3 polyps of which $\geq$ 1 is $\geq$ 1cm).

Non-neoplastic colorectal pathology was defined as pathology which could have potentially accounted for a positive stool test not including adenomatous polyps or colorectal cancer. This included but was not limited to colitis, diverticulitis and haemorrhoids.

In those in whom a diagnosis of colorectal cancer was reached, initial staging for comparison was following endoscopic and imaging modalities. Subsequent, pathological classification in those who underwent operations was by the standard TNM (version 5) classification (Sobin and Fleming 1997). Individuals in whom a polyp cancer was considered to be completely excised and hence did not undergo further colonic resection, were presumed to be node negative and classified as TNM Stage I.

The main outcome measure of the study was the presence of significant neoplasia, which was defined as the presence of either cancer or intermediate or high risk polyps as defined above.

Deprivation category was calculated using the Scottish Index of Multiple Deprivation (SIMD) which is an index of relative deprivation combining 38 indicators across 7 domains, namely: income, employment, health, education, skills and training, housing, geographic access and crime. The overall index is a weighted rank for each domain allowing postcodes to be ranked in order of deprivation across Scotland. Quintiles of deprivation were used to assign patients a relative deprivation category based on their postcode at time of colonoscopy with the first quintile representing the most deprived and the fifth quintile, the least deprived. (SIMD 2009)

Approval for access to data was given by the Caldicott guardian for the data and approved by the local Bowel Screening Steering Group.

Statistical analysis

Associations between categorical variables were examined using χ^2 tests for linear trend unless otherwise specified. Multivariate analysis was performed using binary logistical

regression. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA).

6.3 Results

From invitations sent between April 2009 and March 2011, representing the first complete round in NHS GG&C, 4631 individuals underwent colonoscopy following a positive stool test. Complete results on both outcomes following colonoscopy and bowel symptoms noted at pre-assessment were available for 4182 (90%) patients which formed the basis of our analysis. Of the 4182 patients, 390 (9%) had a diagnosis of cancer and 1964 (47%) had at least one dysplastic polyp identified. Of those with dysplastic polyps 1309 (66%) patients were deemed to have significant polyps, therefore, significant neoplasia was detected in 1699 (41%) individuals.

Overall, 1772 (42%) patients stated they had bowel symptoms of which 1661 (94%) had 1 or more significant bowel symptoms present. Significant symptoms were altered bowel habit (1001 (24%) patients), rectal bleeding (896 (21%) patients), abdominal pain (62 (2%) patients), and tenesmus (8 (0.2%) patients). Symptomatic individuals were more likely to be female (46% vs 35%, $p<0.001$) and younger (46% vs 39% vs 37%, $p<0.001$) (Table 6.1). The presence of symptoms was associated with the absence of significant neoplasia at colonoscopy ($p<0.001$). When individual symptoms were examined, only the presence of altered bowel habit remained significant in predicting those with an absence of significant neoplasia ($p<0.001$) (Table 5.2). On multivariate analysis, the presence of symptoms did not retain significance as being predictive of those without significant neoplasia ($p=0.063$) (Table 6.3).

When those with non-neoplastic colorectal pathology (n=485) were removed from the analysis the presence of significant symptoms remained associated with the absence of significant neoplasia on univariate analysis (OR 0.80 (0.70 – 0.91), $p<0.001$).

In those that had significant neoplasia found at colonoscopy, lesions were confined to the right side of the colon in 207 (12%) patients (Table 6.4). Patients with right sided lesions were less likely to be symptomatic than those with left sided or mixed distribution of lesions ($p=0.044$). Right sided lesions were also associated with an absence of rectal bleeding ($p<0.001$). When adenomas were compared to T1/2 tumours and T3/4 tumours, patients with more advanced disease were more likely to be symptomatic ($p= 0.027$). When the stage distribution of those with colorectal cancer was examined, patients with more advanced tumours were more likely to be symptomatic ($p=0.005$).

6.4 Discussion

The results of the present study showed that in the context of a positive occult blood stool screening test, the presence of significant bowel symptoms was not associated with an increased likelihood of detecting significant colorectal neoplasia. In addition, in those who did have significant neoplasia, lesions were more likely to be more advanced and more distal in those who were symptomatic than those who were asymptomatic.

The results support the hypothesis that individuals who engage in the screening process have a high prevalence of symptoms and that their routine assessment within a screening programme has limited clinical value. This has been shown in three previous studies which have reported symptoms being present in 52% to 78% of those individuals attending for colonoscopy following a positive gFOBt screening test (Ahmed, Leslie et al. 2005; Harmston, Akwei et al. 2010; Saldanha et al. 2013). Our rate of 42% is slightly below these figures and this may be due to the differing demographic profile of the population sampled. Our geographical area encompasses some of the most deprived areas in Scotland and this may have impacted on symptom reporting. Alternately, it may reflect the process of assessing symptoms. Rather than use a proforma, data was collected in free-text form and coded retrospectively. However, as the sample size included in the present study was considerably larger than that of the previous largest study (n=563) this would act to reduce bias (Ahmed, Leslie et al. 2005).

It has been previously postulated that the reason gFOBt positive screening patients have such a high rate of lower GI symptoms is that those who choose to respond to screening invites have a high rate of symptoms (Harmston, Akwei et al. 2010). As such, it has therefore been suggested that rather than identifying truly occult disease, screening represents an additional pathway for symptomatic individuals to present. Providing evidence for this however, would require assessment of symptoms in those who choose not

to respond to a screening invitation. Such a study population would be inherently difficult to assess and therefore such analysis was not carried out.

It was of interest to note the inverse relationship between symptoms and likelihood of significant neoplasia at colonoscopy, a finding which differs from previous studies (Ahmed, Leslie et al. 2005; Harmston, Akwei et al. 2010; Saldanha et al. 2013). This remains when adjustment is made for those patients where significant neoplasia was absent but non-neoplastic colorectal pathology is identified. However, this fails to achieve significance on multivariate analysis when adjustment is made for age, sex and socioeconomic deprivation status. It would be of added interest to examine the hospital attendances and prior investigations of those who were symptomatic but failed to have significant neoplasia found at colonoscopy in the present study. Although individuals underwent a thorough pre-assessment process, it may be that a proportion of the symptomatic individuals were, in fact, inappropriately investigated following a positive screening test and further work is required to explore this concept.

When those who had significant neoplasia were analysed separately there is evidence that symptoms were associated with more advanced and more distal disease. One previous study has examined tumour stage and the presence of symptoms in 200 patients with screen-detected colorectal cancer, however have no clear association with stage was reported (Harmston, Akwei et al. 2010). Comparison with studies examining the link between tumour stage and symptoms in studies performed out with screening is problematic due to the lack of an asymptomatic group for comparison. However, when the duration of symptoms has been studied there is conflicting evidence as to whether a prolonged duration of symptoms is associated with early stage (Jullumstro, Lydersen et al. 2009) or late stage disease (Olsson, Bergkvist et al. 2004). The present study highlights the importance of screening as a tool in detecting early stage disease as only 37% of those with

early stage disease (TNM Stage I & II) had symptoms compared to 47% of those with late stage disease (TNM Stage III & IV).

The present study has accepted limitations in that it is a retrospective analysis of a prospectively collected dataset. The use of a symptom proforma may have increased our symptom detection rate, however this is unlikely to have altered comparisons made within the study group itself. In addition, information regarding additional commonly regarded 'high-risk' symptoms such as weight loss and anaemia were not assessed. These symptoms, however, are not true bowel symptoms and hence were not examined in the context of the present study.

In conclusion, the present study reports a high rate of symptoms in patients undergoing colonoscopy following a positive stool test within the SBoSP, although such symptoms have limited clinical value in predicting the presence of disease. However, in those patients with significant neoplasia, being symptomatic was associated with more advanced tumour stage highlighting the importance of screening in detecting early stage disease.

Table 6.1: The relationship between the presence of significant lower gastrointestinal (GI) symptoms and the presence of significant neoplasia at colonoscopy following a positive screening test

	All patients	Any significant lower GI symptom		p-value
		Absent	Present	
	n(%)	n(%)	n(%)	
	4182	2521	1661	
Age				
≤55	877 (21)	472 (19)	405 (24)	
56-64	1279 (31)	770 (30)	509 (31)	
≥ 65	2026 (48)	1279 (51)	747 (45)	<0.001
Sex				
Female	1695 (40)	900 (36)	795 (48)	
Male	2487 (60)	1621 (64)	866 (52)	<0.001
Deprivation quintile				
1 (most deprived)	1505 (36)	897 (35)	608 (37)	
2	783 (19)	448 (19)	335 (20)	
3	665 (16)	408 (16)	257 (16)	
4	526 (12)	325 (13)	201 (12)	
5 (least deprived)	698 (17)	440 (17)	258 (15)	0.054
Significant neoplasia				
Absent	2483 (59)	1368 (57)	1115 (63)	
Present	1699 (41)	1042 (43)	657 (37)	<0.001

Table 6.2: The relationship between the risk of significant neoplasia at colonoscopy and the presence of significant lower gastrointestinal (GI) symptoms following a positive screening test

	All patients	Risk of significant neoplasia	p-value
	n(%)	OR (95% CI)	
Any significant lower GI symptom			
Absent	2521 (60)	1	
Present	1661 (40)	0.78 (0.69 – 0.89)	<0.001
Rectal bleeding			
Absent	3286 (79)	1	
Present	896 (21)	1.09 (0.93 – 1.26)	0.283
Altered bowel habit			
Absent	3181 (76)	1	
Present	1001 (24)	0.58 (0.50 – 0.68)	<0.001
Abdominal pain			
Absent	4120 (98)	1	
Present	62 (2)	0.80 (0.47 – 1.35)	0.406
Tenesmus			
Absent	4174 (100)	1	
Present	8 (0)	4.40 (0.89 – 21.81)	0.048

Table 6.3: Multivariate analysis of the risk of significant neoplasia at colonoscopy and the presence of significant lower gastrointestinal (GI) symptoms following a positive screening test

	All patients	Risk of significant neoplasia (multivariate analysis)	p-value
	n(%)	OR (95% CI)	
Age			
≤55	877 (21)	1	
56-64	1279 (31)	1.50 (1.25 – 1.81)	<0.001
≥ 65	2026 (48)	1.93 (1.63 – 2.30)	<0.001
Sex			
Female	1695 (40)	1	
Male	2487 (60)	2.20 (1.93 – 2.51)	<0.001
Any significant lower GI symptom			
Absent	2521 (60)	1	
Present	1661 (40)	0.88 (0.77 – 1.01)	0.063

Table 6.4: The relationship between the presence of symptoms and the site and type of lesion in patients with significant neoplasia at colonoscopy following a positive screening test

	All patients with significant neoplasia	Any significant lower GI symptom		p-value	Altered bowel habit		p-value	PR bleeding		p-val
		Absent	Present		Absent	Present		Absent	Present	
	n(%)	n(%)	n(%)		n(%)	n(%)		n(%)	n(%)	
	1699	1083	616		1388	311		1321	378	
Site of lesion										
Right sided	207 (12)	145 (13)	62 (10)		162 (12)	45 (14)		187 (14)	20 (5)	
Left sided/mixed	1492 (88)	938 (87)	554 (90)	0.044	1226 (88)	266 (86)	0.173	1134 (86)	358 (95)	<0.0(
Type of lesion[a]										
Adenoma	1309 (78)	849 (80)	460 (76)		1082 (79)	227 (74)		1025 (79)	284 (77)	
T1/2 tumour	199 (12)	132 (12)	67 (11)		166 (12)	33 (11)		152 (12)	47 (13)	
T3/4 tumour	163 (10)	88 (8)	75 (13)	0.027	119 (9)	44 (15)	0.012	125 (9)	38 (10)	0.51(
TNM Stage[b]										
I	179 (48)	119 (53)	60 (40|)		149 (51)	30 (37)		136 (48)	43 (47)	
II	76 (20)	42 (19)	34 (23)		56 (19)	20 (25)		59 (21)	17 (19)	
III	95 (25)	55 (24)	40 (27)		74 (25)	21 (26)		75 (26)	20 (22)	
IV	26 (26)	9 (4)	17 (11)	0.005	16 (5)	10 (12)	0.025	14 (13)	12 (13)	0.29(

[a] n = 1671 [b] n = 376

7 A COMPARISON OF TUMOUR AND HOST PROGNOSTIC FACTORS IN SCREEN-DETECTED VERSUS NON SCREEN-DETECTED COLORECTAL CANCER: A CONTEMPORANEOUS STUDY

7.1 Introduction

Independent of stage at presentation, there are other additional adverse features of both the tumour itself and the individual who develops the disease, the so called 'host', that have been shown to be predictive of a worse outcome. For example, adverse tumour features, such as the presence of poor differentiation, venous invasion, resection margin status, tumour perforation and serosal involvement are all indicative of poorer cancer specific survival and should be included in pathological reporting of specimens (Compton, Fielding et al. 2000; Petersen, Baxter et al. 2002). These are now used in clinical practice to help identify patients with more aggressive TNM Stage II disease that are at a higher risk of recurrence and hence may benefit from adjuvant chemotherapy (Figueredo, Coombes et al. 2008). Indeed, it has been argued recently that the combination of T-stage and venous invasion is superior to the tradition TNM stage in predicting outcome in node negative disease (Roxburgh, McMillan et al. 2014).

With consideration to host factors, there is now a wealth of evidence that the presence of an elevated host systemic inflammatory response (SIR) is an independent negative prognostic factor in patients with cancer (McAllister and Weinberg 2014). In particular, in those undergoing resection for colorectal cancer those with an elevated pre-operative SIR have a worse outcome (Roxburgh and McMillan 2010). The SIR can be assessed routinely with standard bedside tests such as C-reactive protein (CRP) or the neutrophil to lymphocyte ratio (NLR)(Walsh, Cook et al. 2005; Ishizuka, Nagata et al. 2007; Proctor,

Morrison et al. 2011; Li, Liu et al. 2014). Such patients with an elevated SIR have poorer cancer-specific mortality independent of TNM stage (Crozier, McKee et al. 2006).

Screening for colorectal cancer using the guaiac-based faecal occult blood test (gFOBt) increases the number of early stage cancers diagnosed and reduces cancer specific mortality (Hardcastle, Chamberlain et al. 1996; Kronborg, Fenger et al. 1996; Hewitson, Glasziou et al. 2007). In addition, there is increasing evidence that screening using the faecal immunochemical test (FIT), where the level of blood in the stool can be quantified, may have improved sensitivity over gFOBt, (Guittet, Bouvier et al. 2007; Hol, Wilschut et al. 2009; Parra-Blanco, Gimeno-Garcia et al. 2010). This has lead to the development of the Scottish Bowel Screening Programme (SBoSP), which is a gFOBt/FIT population based screening programme, where individuals with a weakly positive result on initial gFOBt testing are sent a confirmatory FIT (Fraser, Digby et al. 2012). This has been found to detect a large number of early stage tumours, however interval cancers do develop (Steele, McClements et al. 2012). In the context of a biennial screening programme, interval cancers are tumours that develop within 2 years of a negative screening test. This number appears to increase with successive screening rounds, suggesting that while screening is good at targeting so called screen-detected cancers, a proportion of tumours are resistant to the screening process in its current form (Steele, McClements et al. 2009; Steele, McClements et al. 2012).

In the context of assessing colorectal cancer screening efficacy, previous work has examined differences between screen-detected and non screen-detected disease and have shown improved survival in screen-detected patients (Courtney, Chong et al. 2013; Gill, Bramble et al. 2012; Libby, Brewster et al. 2012; Mackay, Ramsay et al. 2012; Morris, Whitehouse et al. 2012; Pande, Froggatt et al. 2013; Roxburgh, McTaggart et al. 2013). However, such analysis has focused on stage and site of tumours and only one such paper

has included detailed analysis of adverse tumour factors beyond TNM stage that are of independent prognostic significance (Roxburgh, McTaggart et al. 2013). Furthermore, to date, no previous studies have included assessment of the pre-operative host systemic inflammatory response within the context of a colorectal cancer screening programme.

The aim of the present study was to examine the efficacy of the first round of a population based gFOBt/FIT colorectal cancer screening programme in our geographical area with regards to cancer detection rates, and to compare and contrast adverse tumour and host prognostic factors in screen-detected and non screen-detected colorectal cancer.

7.2 Materials and methods

Details for all individuals who were invited to the first round of the SBoSP during April 2009 to the end of March 2011 in NHS Greater Glasgow & Clyde (NHS GG&C) were extracted from the prospectively maintained NHS GG&C Bowel Screening IT System (original date of extraction January 2012, updated April 2014). Methodology data on the screening algorithm and processing of samples of the SBoSP has been described in previous Chapters (Fraser, Digby et al. 2012). Data on individual outcomes from screening invite, combined gFOBt/FIT result, uptake of colonoscopy and outcome from colonoscopy were extracted.

All individuals invited to screening in this first round were cross-referenced with the prospectively maintained West of Scotland Colorectal Cancer Managed Clinical Network (MCN) dataset and also linked to the Scottish Cancer Registry (SMR06). This allowed comprehensive identification of any patient with a diagnosis of colorectal cancer. As screening invitations are biennial, patients with cancer detected more than 720 days after screening invite were excluded. Patients with colorectal cancer were then categorised as having screen-detected disease (SD), or non screen-detected disease (NSD). NSD patients were then further sub-characterised as being non-responders to the screening invitation (NR), having an interval cancer detected following a negative gFOBt/FIT (INT), having a cancer in patient who tested positive but did not attend for colonoscopy (NA) or a cancer in a patient who did not have cancer detected at screening colonoscopy (CN). Patients who had an initial suspicious adenomatous polyp detected through screening and as a result of subsequent investigations had colorectal cancer detected within 6 months of screening invite were termed SD.

Individual patient records were then interrogated on a case-by-case basis to identify further clinicopathological variables for analysis. Tumours were staged according to the

conventional tumour node metastasis (TNM) classification (5th Edition)(Sobin and Fleming 1997). In those who did not undergo a resection, staging was determined from endoscopic and imaging modalities. Individuals in whom a polyp cancer was considered to be completely excised endoscopically and hence did not undergo further colonic resection, were presumed to be node negative and classified as TNM Stage I. Additional high-risk tumour features were identified from pathology reports.

Both the absolute neutrophil count and the neutrophil to lymphocyte ratio (NLR) were used as a markers of the pre-operative SIR and were obtained from pre-operative blood results taken most immediately and not more than 6 weeks prior to surgery. With regards the NLR, a previously validated threshold of $\geq$5 was used as being evidence of a significantly elevated SIR (Walsh, Cook et al. 2005). An absolute neutrophil level greater than 7.5 x 10^9 was defined as elevated as per local laboratory guidelines.

Deprivation category was calculated using the Scottish Index of Multiple Deprivation (SIMD) which is an index of relative deprivation combining 38 indicators across 7 domains, namely: income, employment, health, education, skills and training, housing, geographic access and crime. The overall index is a weighted rank for each domain allowing postcodes to be ranked in order of deprivation across Scotland. Quintiles of deprivation were used to assign patients a relative deprivation category based on their postcode at time of colonoscopy with the first quintile representing the most deprived and the fifth quintile, the least deprived (SIMD 2009).

Permission for the study was granted by both the Caldicott Guardian of the Screening dataset and by the West of Scotland Colorectal Cancer MCN Management group. Data was stored and analysed in an anonymised manner.

Statistical analysis

Associations between categorical variables were examined using the χ^2 test. For ordered variables with multiple categories the χ^2 test for linear trend was used. Fishers exact test was used for assessing associations where individual cell counts were less than 5. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA)

7.3 Results

From April 2009 to March 2011, representing the first complete round of screening in NHS GG&C, 395 097 individuals were invited to participate, 204 535 (52%) responded and 6 159 (3.0%) tested positive. Of those who tested positive, 4 797 (78%) individuals proceeded to undergo colonoscopy and 421 patients had cancer detected (SD) (Figure 7.1). These figures differ slightly from previous chapters due to updating of the data within the Bowel Screening IT System and a later date of extraction for this chapter. After cross-referencing with MCN and SMR06 datasets, 708 patients with NSD colorectal cancer were identified (468 (65%) patients NR; 182 (25%) patients INT, 43 (6%) patients NA; 15 (2%) patients CN). This generated an estimated sensitivity and specificity of the first round of the gFOBt/FIT screening test of 72.4% and 97.2% respectively (Table 7.1).

Comparison of Screen-detected and Non Screen-detected Colorectal cancer

Comparing SD and NSD patients, SD patients were more likely to be male ($p=0.002$), less deprived ($p=0.001$), have more distal disease ($p=0.003$), which was of an earlier stage ($p<0.001$) and were more likely to undergo a procedure with a curative intent ($p<0.001$) than NSD patients (Table 7.2). When high-risk tumour features were examined in those undergoing a curative procedure, SD patients had a less advanced T-stage, less evidence of venous invasion, peritoneal involvement and margin involvement ($p<0.05$). They also had less evidence of an elevated pre-operative SIR as evidence by both the NLR and the absolute neutrophil count (Table 7.3). Stage by stage analysis of factors was then carried out (Table 7.4). Patients with SD tumours had less evidence of an elevated SIR in stage II and III disease. There was no significant difference in venous invasion rates between SD and NSD tumours across all 4 stages (Table 7.4).

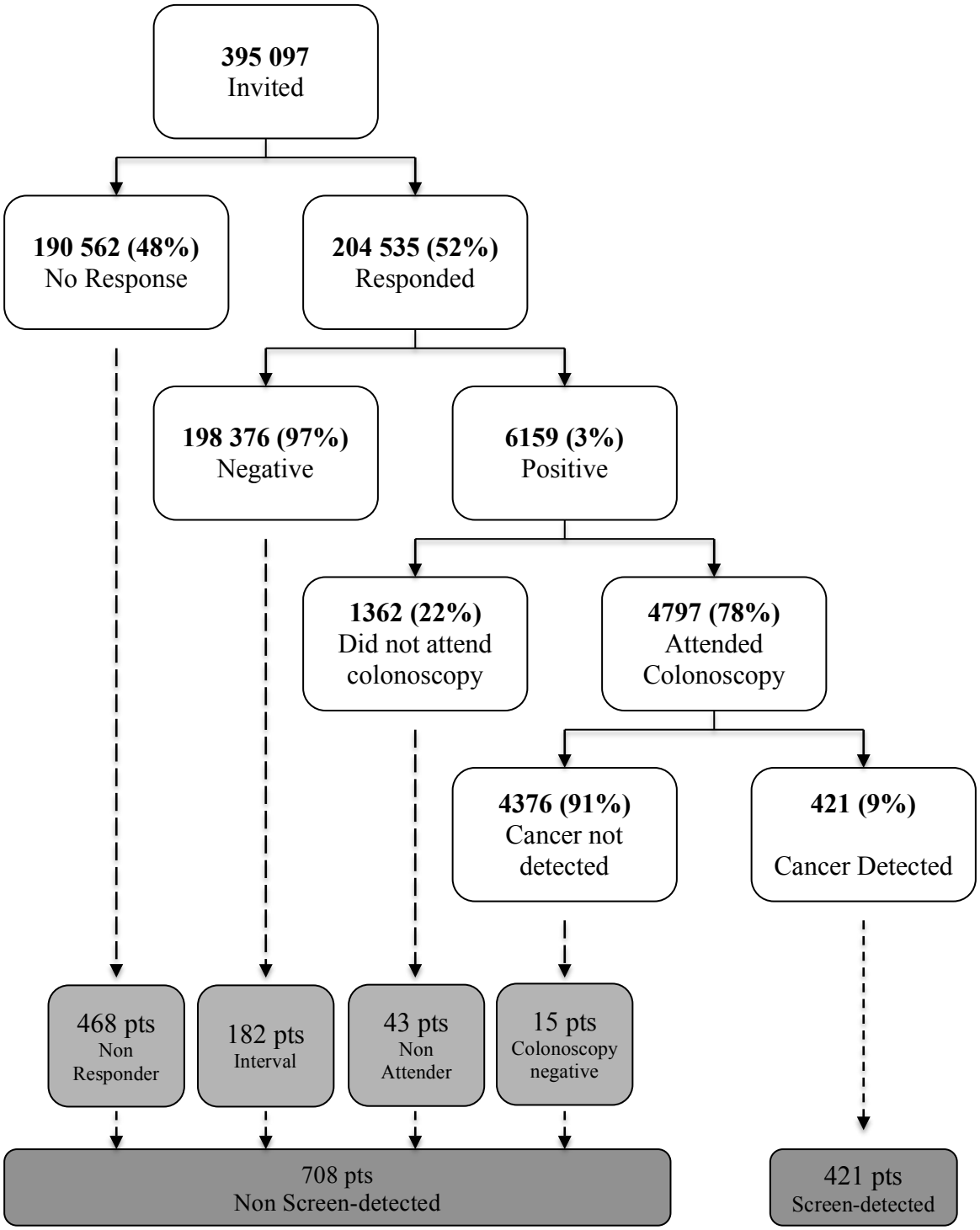


Figure 7.1: Outcome from the 1st round of the Scottish Bowel Screening Programme in NHS GG&C

Comparison of Interval and Screen-detected Cancers

Sub analysis of NSD patients was undertaken to examine INT patients in more detail. Comparing INT and SD patients, INT patients were more likely to be female ($p<0.001$), have more proximal disease ($p<0.001$), have more advanced disease ($p<0.001$) and less likely to be managed with a curative intent ($p<0.001$) (Table 6.5). In addition, they were more likely to have adverse prognostic factors such as venous invasion ($p=0.026$) and an elevated pre-operative SIR ($p=0.025$) (Table 6.6). However, on stage by stage analysis these differences failed to retain significance. In particular, venous invasion rates were similar across Stage 1 (17% INT vs 25% SD, $p=0.344$), Stage II (57% INT vs 47% SD, $p=0.272$) and Stage III (71% INT vs 70% SD, $p=0.970$) disease.

Comparison of Interval and Non-Responder Cancers

Comparing INT and NR patients, INT patients were more likely to be female ($p=0.034$) and less deprived ($p<0.001$) than NR patients (Table 6.7). There was trend towards INT patients having less advanced ($p=0.052$) and more proximal disease ($p=0.090$) however this did not reach significance. When those who were treated with a curative intent were examined, there was no difference in adverse pathological features between INT and NR patients. There was a trend for NR patients have an elevated pre-operative SIR ($p=0.059$) compared to INT patients (Table 6.8).

7.4 Discussion

The results of the present study provide a comprehensive analysis of the outcomes from the first round of a stool-based colorectal cancer screening programme. It confirms previous studies that have found that screen-detected tumours are of an earlier stage than non screen-detected tumours, and reports, for the first time, that within Stage II and III disease, individuals with screen-detected tumours have more favourable host prognostic factors than those with non screen-detected tumours.

Analysis of host factors, such as the presence of an elevated SIR has not previously been examined within the context of a colorectal cancer screening programme. The present study reports higher levels of systemic inflammation in patients with NSD tumours and this is not unsurprising as the SIR has been linked with tumour size (Crozier, McMillan et al. 2007). However, this difference remains when adjusted for stage in Stage II and Stage III disease. The presence of an elevated SIR has also been associated with increased deprivation (Roxburgh, Platt et al. 2011), increased pre-operative co-morbidity (Roxburgh, Platt et al. 2011) and higher rates of emergency presentation (Crozier, Leitch et al. 2009). It is unclear whether a higher rate of elevated host SIR in the NSD group may reflect patients who are more deprived and have more co-morbidities than those in the SD group. However, it has previously been shown that patients who are diagnosed with colorectal cancer through screening have a lower American Society of Anaesthesiologist (ASA) grade when compared to patients who do not respond to a screening invite (Gill, Bramble et al. 2012). Furthermore it has been reported that screening reduces the rate of emergency presentation and such a factor may be involved (Scholefield, Robinson et al. 1998; Goodyear, Leung et al. 2008). Further work exploring why SD patients have lower levels of inflammation than NSD patients is required and should involve full assessment of patient comorbidities.

It was interesting to note that within Stage I disease no differences between tumour and host factors between SD and NSD disease was identified, despite similar numbers to Stage II and III disease. This would be in keeping with the natural history of solid organ tumours whereby tumour heterogeneity develops as the lesion progresses. It is known that patients with Stage II and III disease represent a spectrum of disease with varied outcomes, whereas patients undergoing resection with Stage I disease have consistently better results.

One of the criticisms of screening and analysis of data from screening programmes is that it can introduce two clear forms of bias (Kay and Witte 1991). The first is lead-time bias, where an earlier diagnosis of cancer in a pre-symptomatic phase artificially elongates an individual's cancer-specific survival without altering that individual's date of death. Secondly there is length time-bias, where the identification of indolent slow growing tumours artificially improves cancer-specific survival by detecting those who have a longer pre-clinical phase. The extreme form of length-time bias is overdiagnosis, whereby screening detects and eliminates tumours that may not have become apparent within a patients lifetime(Kay and Witte 1991). There is evidence from breast cancer screening that such overdiagnosis occurs, with a higher incidence of cancer being diagnosed in those who are invited to screening when followed up over 10 years (Allgood, Duffy et al. 2011).

It could be argued that the present study, showing that some adverse tumour prognostic factors are less prevalent in SD tumours than in NSD tumours, is evidence for the effect of length-time bias. However, when adjustment is made for stage, the two key features in keeping with phenotypically more aggressive tumours, venous invasion and poor differentiation, do not achieve significance. Therefore, the conclusion that can be drawn from the present study is that the inherent biological characteristics of SD tumours do not differ from those of NSD disease. Furthermore, if length-time bias were to be the case in colorectal cancer screening, then a higher incidence of colorectal cancer in individuals

invited to screening would have been seen in long-term follow-up of gFOBt randomised control trials. This was not the case, for example, in the Nottingham gFOBt trial, similar incidence rates of cancer were seen between those in the screened and control groups (Scholefield, Moss et al. 2012). Both the Scottish and English bowel screening programmes are still relatively immature and as such, effects of the population programmes on incidence at a national level are yet to be examined.

Within analysis of patients with NSD disease it is interesting to examine INT cancers in more detail as they are indicative of the sensitivity of a screening programme. The present study represents the first time the sensitivity and specificity of the current SBoSP algorithm has been examined in a population setting. In the present study, of the 661 patients who developed cancer in those who responded to screening, 182 (28%) were gFOBt/FIT negative. A similar INT cancer rate of 30% was reported in the first round the Scottish gFOBt pilot study. This is perhaps surprising as this suggests that the present gFOB/FIT algorithm does not confer a significant advantage over the gFOBt programme with regards test characteristics. Further work analysing INT cancer rates over subsequent rounds will be required to assess the true influence of the change from the gFOBt to a gFOBt/FIT pathway.

There is evidence that the level of haemoglobin present within an individuals stool is affected by individual demographics such as age, sex and deprivation (Digby, McDonald et al. 2014; Fraser, Rubeca et al. 2014). In particular older, males, who are more deprived have demonstrably higher levels of haemoglobin in their faeces. The results of the present study confirm that this can translate clinically into higher rates of INT tumours in females compared to males. There was, however, no difference in deprivation noted between individuals with SD and INT tumours in the present study. There are currently proposals to develop quantitative FIT as a first line test within the SBoSP and there will be the

opportunity to adjust positive thresholds for specific patient demographics (Steele, McDonald et al. 2013). Further work, in larger numbers, is required to establish whether the detected difference in faecal haemoglobin levels within deprivation quintiles, will translate in to practice with the development of less INT tumours in those who are deprived.

It has previously been postulated that INT tumours do not only represent tumours missed by the screening test itself but that they may be more aggressive tumours that develop within the screening interval (Gill, Bramble et al. 2012; Steele, McClements et al. 2012). The present study is the first to examine in detail tumour and host prognostic factors and provides evidence to refute this hypothesis. There was no evidence of adverse tumour features in the INT group when compared to the NR group in the present study. Indeed, there was a trend for NR patients to have evidence of a higher host SIR.

There were higher than expected number of cancers in both the NA and CN groups. However, on further investigation it became apparent that a substantial proportion of the NA patients (40%, data not presented), were already under investigation for colorectal symptoms and had sent back the screening test in the midst of undergoing non-screening investigations. Also, of the 15 patients who were CN, 12 (80%) patients (data not presented) had polyps detected at colonoscopy and hence were undergoing follow-up. For the purposes of the present study, a cancer diagnosis outwith 6 months of initial colonoscopy was defined as NSD, however it may be argued that these patients would not have been detected at that time had they not participated in screening. Accounting for that, there were however, 3 patients who had normal colonoscopies and hence could be defined as having true post-colonoscopy colorectal cancer. This figure compares favourably to other studies that have examined this outwith screening programmes and have provided rates of 2- 8% albeit with longer (3 to 5 year) follow-up (Bressler, Paszat et al. 2007;

Singh, Nugent et al. 2010; le Clercq, Bouwens et al. 2014). The majority of post-colonoscopy colorectal cancers are thought to arise through procedural factors such as missed lesions and inadequate examination (le Clercq, Bouwens et al. 2014). The SBoSP has tight quality control measures with all colonoscopists requiring to be Joint Advisory Group (JAG) accredited and have a greater than 90% completion rate (QIS 2007). It was outwith the scope of the present study to examine colonoscopy quality indexes in more detail, however, the low rate of true post-colonoscopy colorectal cancer was reassuring.

The main strengths of the present study include the comprehensive and detailed dataset. Case notes were examined on a cases-by-case basis allowing for more detailed analysis of clinicopathological factors at a level of granularity that has not previously been undertaken. For example, in the present study after case note review, only 2% of tumours remained unstaged compared to 25% in a previous study utilising population databases (Morris, Whitehouse et al. 2012). In addition, we have included data from non-responders, which has been absent from other studies, and by utilising both regional and national cancer registry datasets have comprehensively captured those with NSD disease from corroborative sources.

The main limitation of the study is the fact that this is a prevalence round of a screening programme and as such these results may not be applicable in subsequent rounds. This is important when analysing data presented regarding sensitivity and specificity. It is important to consider that population screening tests for colorectal cancer, using either gFOBt or FIT are designed to be repeated on a regular basis and therefore analysing a solitary round in isolation is not necessarily indicative of the efficacy of the programme as a whole. Finally, our measure of the SIR was using NLR and not mGPS, which has been shown to be a more sensitive measure of host inflammation with regards outcome (Proctor, Morrison et al. 2011). However, this is a retrospective study, and C-reactive protein,

required for calculating mGPS, was not routinely measured pre-operatively across all hospitals during this timeframe.

In conclusion, the present study reports that within Stage II and III disease, individuals with SD tumours had more favourable host prognostic factors than patients with NSD tumours. However, there was no difference in adverse tumour features associated with an aggressive tumour phenotype. In addition, INT cancers do not appear to have more aggressive features than tumours that develop in the rest of the population and hence are more likely to arise as a result of the limitations of the testing algorithm itself rather than represent biologically more aggressive tumours. Further work, identifying a more sensitive test is required in order to increase the number of tumours that are detected through screening and hence improve outcomes in colorectal cancer.

Table 7.1: Estimation of sensitivity & specificity of the 1st round of the Scottish Bowel Screening Programme in Greater Glasgow & Clyde

		Combined gFOBt/FIT screening test		
		Positive	**Negative**	**TOTAL**
Colorectal Cancer	**Present**	479	182	661
	Absent	5680	198 194	203 874
	TOTAL	6159	198 376	204 535

Sensitivity = 479 / 661 = 72.4 %
Specificity = 198 194 / 203 874 = 97.2 %

Table 7.2: Baseline characteristics of Screen-detected and Non Screen-detected Colorectal Cancer (all patients)

	All patients n(%)	Screen-detected n(%)	Non Screen-detected n(%)	p-value
	1129	421	708	
Age				
<64	437 (39)	164 (39)	273 (39)	
64 – 70	300 (27)	114 (27)	186 (26)	
>70	392 (35)	143 (34)	249 (35)	0.762
Sex				
Female	447 (40)	142 (34)	305 (43)	
Male	682 (60)	279 (66)	403 (57)	0.002
Deprivation quintile				
1 (most deprived)	403 (36)	125 (30)	278 (39)	
2	199 (18)	71 (17)	128 (18)	
3	182 (16)	78 (19)	104 (15)	
4	151 (13)	67 (16)	84 (12)	
5 (least deprived)	189 (17)	78 (19)	111 (16)	0.001
Site				
Proximal to splenic flexure	325 (29)	100 (24)	225 (32)	
Distal to splenic flexure	795 (71)	321 (76)	474 (67)	0.003
Synchronous	9 (1)	0	9 (1)	
TNM Stage				
I	318 (28)	191 (45)	127 (18)	
II	285 (25)	93 (22)	192 (27)	
III	284 (25)	103 (25)	181 (26)	
IV	220 (20)	28 (7)	192 (27)	<0.001
Unstaged	22 (2)	6 (1)	16 (2)	
Management intent				
Curative procedure	872 (77)	393 (93)	479 (68)	
Palliative procedure	102 (9)	8 (2)	94 (13)	<0.001
No procedure	155 (14)	20 (5)	135 (19)	

Table 7.3: Comparison of tumour and host prognostic factors between Screen-detected and Non Screen-detected Colorectal Cancer (patients undergoing a procedure with a curative intent)

	All patients	Screen-detected	Non Screen-detected	p-value
	n(%) 872	n(%) 393	n(%) 479	
Age				
<64	350 (40)	148 (38)	202 (42)	
64 – 70	221 (25)	107 (27)	114 (24)	
>70	301 (35)	138 (35)	163 (34)	0.340
Sex				
Female	346 (60)	135 (34)	211 (44)	
Male	526 (60)	258 (66)	268 (56)	0.004
Deprivation quintile				
1 (most deprived)	288 (33)	115 (29)	173 (36)	
2	161 (19)	68 (17)	93 (20)	
3	144 (17)	71 (18)	73 (15)	
4	123 (14)	63 (16)	60 (13)	
5 (least deprived)	154 (17)	75 (19)	79 (17)	0.016
Site				
Proximal to splenic flexure	240 (27)	94 (24)	146 (30)	
Distal to splenic flexure	626 (72)	299 (76)	327 (69)	0.023
Synchronous	6 (1)	0	6 (1)	
T-stage				
0/1	233 (27)	149 (38)	84 (18)	
2	124 (14)	63 (16)	61 (13)	
3	365 (42)	153 (39)	212 (44)	
4	150 (17)	28 (7)	122 (26)	<0.001
N-stage[a]				
0	522 (66)	228 (69)	294 (64)	
1	182 (23)	73 (22)	109 (24)	
2	89 (11)	32 (10)	57 (12)	0.138
Differentiation[b]				
Poor	69 (8)	24 (6)	45 (10)	
Moderate/well	795 (92)	368 (94)	427 (90)	0.066
Venous Invasion[c]				
Present	405 (50)	163 (44)	242 (55)	
Absent	413 (50)	213 (57)	200 (45)	0.001
Peritoneal involvement[a]				
Present	128 (16)	20 (6)	108 (24)	
Absent	665 (84)	313 (94)	352 (77)	<0.001
Tumour Perforation[a]				
Present	39 (5)	4 (1)	35 (8)	
Absent	754 (95)	329 (98)	425 (92)	<0.001
Margin Involvement[a]				
Present	27 (3)	5 (2)	22 (5)	
Absent	766 (97)	328 (98)	438 (95)	0.012
Absolute neutrophil count[d]				
>7.5	70 (9)	13 (4)	57 (13)	
≤7.5	710 (91)	315 (96)	395 (87)	<0.001
Neutrophil/lymphocyte ratio[d]				
≥ 5	123 (16)	28 (9)	95 (21)	
< 5	657 (84)	300 (91)	357 (79)	<0.001

[a.]n=793, [b]n= 866, [c]n= 818, [d]n=780

Table 7.4a: Comparison of tumour and host prognostic factors, stratified by TNM stage (patients undergoing resection with a curative intent TNM stage I)

Stage		All patients n(%)	Screen-detected n(%)	Non Screen-detected n(%)	p-value
I		237	131	106	
	Age				
	<64	102 (43)	55 (42)	47 (44)	
	64 – 70	64 (27)	41 (31)	23 (22)	
	>70	71 (30)	35 (27)	36 (34)	0.658
	Sex				
	Female	94 (40)	44 (34)	50 (47)	
	Male	143 (60)	87 (66)	56 (53)	0.034
	Deprivation quintile				
	1 (most deprived)	71 (30)	38 (29)	33 (31)	
	2	43 (18)	24 (18)	19 (18)	
	3	39 (17)	26 (20)	13 (12)	
	4	35 (15)	19 (15)	16 (15)	
	5 (least deprived)	49 (21)	24 (18)	25 (24)	0.715
	Site				
	Proximal to splenic flexure	41 (17)	23 (18)	18 (17)	
	Distal to splenic flexure	196 (82)	108 (82)	88 (83)	0.907
	Synchronous	0	0	0	
	Differentiation[a]				
	Poor	8 (5)	5 (4)	3 (3)	
	Moderate/well	225 (95)	125 (96)	100 (97)	0.250
	Venous Invasion[b]				
	Present	60 (29)	33 (27)	27 (32)	
	Absent	147 (71)	89 (73)	58 (68)	0.463
	Peritoneal involvement				
	Present	1 (0)	1 (1)	0	
	Absent	236 (100)	130 (99)	106 (100)	0.368
	Tumour Perforation				
	Present	2 (1)	2 (1)	0	
	Absent	235 (99)	129 (99)	106 (100)	0.202
	Margin Involvement				
	Present	0	0	0	
	Absent	237 (100)	131 (100)	106 (100)	
	Absolute neutrophil count[c]				
	>7.5	4 (2)	2 (2)	2 (2)	
	≤7.5	228 (98)	126 (98)	102 (98)	0.834
	Neutrophil/lymphocyte ratio[c]				
	≥ 5	16 (7)	8 (6)	8 (8)	
	< 5	216 (93)	120 (94)	96 (92)	0.667

[a]n=232, [b]n=207, [c]n=232

Table 7.4b: Comparison of tumour and host prognostic factors, stratified by TNM stage (patients undergoing resection with a curative intent TNM stage II)

Stage		All patients	Screen-detected	Non Screen-detected	p-value
		n(%)	n(%)	n(%)	
II		270	91	179	
	Age				
	<64	91 (34)	28 (31)	63 (35)	
	64 – 70	71 (26)	25 (28)	46 (26)	
	>70	108 (40)	38 (42)	70 (39)	0.522
	Sex				
	Female	124 (46)	40 (44)	84 (47)	
	Male	146 (54)	51 (56)	95 (53)	0.644
	Deprivation quintile				
	1 (most deprived)	104 (39)	26 (29)	78 (44)	
	2	47 (17)	11 (12)	36 (20)	
	3	47 (17)	21 (23)	26 (15)	
	4	34 (13)	18 (20)	16 (9)	
	5 (least deprived)	38 (14)	15 (16)	23 (13)	0.003
	Site				
	Proximal to splenic flexure	107 (40)	38 (42)	69 (39)	
	Distal to splenic flexure	160 (59)	53 (58)	107 (60)	0.687
	Synchronous	3(1)	0	3 (2)	
	Differentiation				
	Poor	18 (7)	4 (4)	14 (8)	
	Moderate/well	252 (93)	87 (96)	165 (92)	0.287
	Venous Invasion[d]				
	Present	134 (50)	42 (47)	92 (52)	
	Absent	133 (50)	48 (53)	85 (48)	0.413
	Peritoneal involvement				
	Present	48 (18)	7 (8)	41 (23)	
	Absent	222 (82)	84 (92)	138 (77)	0.002
	Tumour Perforation				
	Present	20 (7)	1 (1)	19 (11)	
	Absent	250 (93)	90 (99)	160 (89)	0.005
	Margin Involvement				
	Present	11 (4)	1 (1)	10 (6)	
	Absent	259 (96)	90 (99)	169 (94)	0.078
	Absent neutrophil count[e]				
	>7.5	35 (13)	5 (6)	30 (17)	
	≤7.5	233 (87)	86 (94)	147 (83)	0.007
	Neutrophil/lymphocyte ratio[e]				
	≥ 5	48 (18)	8 (9)	40 (23)	
	< 5	220 (82)	83 (91)	137 (77)	0.005

[d]n=267, [e]n=268

Table 7.4c: Comparison of tumour and host prognostic factors, stratified by TNM stage (patients undergoing resection with a curative intent TNM stage III)

Stage		All patients n(%)	Screen-detected n(%)	Non Screen-detected n(%)	p-value
III		244	101	143	
	Age				
	<64	112 (46)	42 (42)	70 (49)	
	64 – 70	58 (24)	25 (25)	33 (23)	
	>70	74 (30)	34 (34)	40 (28)	0.243
	Sex				
	Female	90 (37)	31 (31)	59 (41)	
	Male	154 (63)	70 (69)	84 (59)	0.093
	Deprivation quintile				
	1 (most deprived)	74 (31)	36 (36)	38 (27)	
	2	45 (19)	17 (17)	28 (20)	
	3	40 (16)	14 (14)	26 (18)	
	4	39 (16)	13 (13)	26 (18)	
	5 (least deprived)	44 (18)	20 (20)	25 (17)	0.446
	Site				
	Proximal to splenic flexure	76 (31)	31 (31)	45 (31)	
	Distal to splenic flexure	165 (68)	70 (69)	95 (66)	0.811
	Synchronous	3 (1)	0	3 (2)	
	Differentiation[f]				
	Poor	34 (14)	13 (13)	21 (14)	
	Moderate/well	209 (86)	88 (87)	121 (85)	0.348
	Venous Invasion[g]				
	Present	161 (69)	69 (70)	92 (68)	
	Absent	72 (31)	29 (30)	43 (32)	0.713
	Peritoneal involvement				
	Present	58 (24)	11 (11)	47 (33)	
	Absent	186 (76)	90 (89)	96 (67)	<0.001
	Tumour Perforation				
	Present	10 (4)	1 (1)	9 (6)	
	Absent	234 (96)	100 (99)	134 (94)	0.040
	Margin Involvement				
	Present	11 (5)	4 (4)	7 (5)	
	Absent	233 (95)	97 (96)	136 (95)	0.729
	Absent neutrophil count[h]				
	>7.5	24 (10)	6 (6)	18 (13)	
	≤7.5	211 (90)	92 (94)	119 (87)	0.081
	Neutrophil/lymphocyte ratio[h]				
	≥ 5	48 (20)	11 (11)	37 (27)	
	< 5	187 (80)	87 (89)	100 (73)	0.003

[f]n=243, [g]n=233, [h]n=235

Table 7.5: Comparison of baseline characteristics Interval and Screen-detected cancers (all patients)

	Interval n(%)	Screen-detected n(%)	*p-value*
	182	421	
Age			
<64	64 (35)	164 (39)	
64 – 70	59 (32)	114 (27)	
>70	59 (32)	143 (34)	0.765
Sex			
Female	91 (50)	142 (34)	
Male	91 (50)	279 (66)	<0.001
Deprivation quintile			
1 (most deprived)	61 (34)	125 (30)	
2	23 (13)	71 (17)	
3	30 (17)	78 (19)	
4	26 (14)	67 (16)	
5 (least deprived)	42 (23)	78 (19)	0.758
Site			
Proximal to splenic flexure	69 (38)	100 (24)	
Distal to splenic flexure	113 (62)	321 (76)	<0.001
Synchronous	0	0	
TNM Stage			
I	37 (20)	191 (45)	
II	45 (25)	93 (22)	
III	53 (29)	103 (25)	
IV	46 (25)	28 (7)	<0.001
Unstaged	1 (1)	6 (1)	
Management intent			
Curative procedure	130 (71)	393 (93)	
Palliative procedure	20 (11)	8 (2)	
No procedure	32 (18)	20 (5)	<0.001

Table 7.6: Comparison of tumour and host prognostic factors in Interval and Screen-detected cancers (patients undergoing a procedure with a curative intent)

	Interval n(%)	Screen-detected n(%)	*p-value*
	130	393	
Age			
<64	44 (34)	148 (38)	
64 – 70	40 (31)	107 (27)	
>70	46 (35)	138 (35)	0.634
Sex			
Female	63 (49)	258 (66)	
Male	67 (52)	135 (34)	<0.001
Deprivation quintile			
1 (most deprived)	36 (28)	115 (29)	
2	18 (14)	68 (17)	
3	24 (19)	71 (18)	
4	21 (16)	63 (16)	
5 (least deprived)	31 (24)	75 (19)	0.285
Site			
Proximal to splenic flexure	45 (35)	94 (24)	
Distal to splenic flexure	85 (65)	299 (76)	0.017
Synchronous	0	0	
T-stage			
0/1/2	43 (33)	212 (54)	
3/4	87 (67)	181 (46)	<0.001
N-stage[a]			
0	77 (61)	228 (69)	
1/2	49 (39)	105 (32)	0.137
Differentiation[b]			
Poor	13 (10)	24 (6)	
Moderate/well	114 (90)	368 (94)	0.118
Venous Invasion[c]			
Present	68 (55)	163 (43)	
Absent	56 (45)	213 (57)	0.026
Absolute neutrophil count[d]			
≥7.5	12 (9)	13 (4)	
<7.5	115 (91)	315 (96)	0.021
Neutrophil/lymphocyte ratio[d]			
≥ 5	20 (16)	28 (9)	
< 5	107 (84)	300 (91)	0.025

[a] n=459, [b]n=519, [c]n=500, [d]n=455.

Table 7.7: Comparison of baseline characteristics Interval and Non-responder cancers (all patients)

	Interval n(%)	Non-responder n(%)	*p-value*
	182	468	
Age			
<64	64 (35)	188 (40)	
64 – 70	59 (32)	113 (24)	
>70	59 (32)	167 (36)	0.816
Sex			
Female	91 (50)	191 (41)	
Male	91 (50)	277 (59)	0.034
Deprivation quintile			
1 (most deprived)	61 (34)	196 (42)	
2	23 (13)	90 (19)	
3	30 (17)	71 (15)	
4	26 (14)	54 (12)	
5 (least deprived)	42 (23)	54 (12)	<0.001
Site			
Proximal to splenic flexure	69 (38)	142 (31)	
Distal to splenic flexure	113 (62)	317 (69)	0.090
Synchronous			
TNM Stage			
I	37 (20)	74 (16)	
II	45 (25)	130 (28)	
III	53 (29)	115 (25)	
IV	46 (25)	135 (29)	0.052
Unstaged	1 (1)	14 (3)	
Management intent			
Curative procedure	130 (71)	306 (65)	
Palliative procedure	20 (11)	67 (14)	
No procedure	32 (18)	95 (20)	0.210

Table 7.8: Comparison of tumour and host prognostic factors in Interval and Non-responder cancers (patients undergoing a procedure with a curative intent)

	Interval n(%)	Non-responder n(%)	p-value
	130	306	
Age			
<64	44 (34)	140 (46)	
64 – 70	40 (31)	63 (21)	
>70	46 (35)	103 (34)	0.135
Sex			
Female	63 (49)	178 (58)	
Male	67 (52)	128 (42)	0.062
Deprivation quintile			
1 (most deprived)	36 (28)	123 (40)	
2	18 (14)	63 (21)	
3	24 (19)	47 (15)	
4	21 (16)	35 (12)	
5 (least deprived)	31 (24)	37 (12)	<0.001
Site			
Proximal to splenic flexure	45 (35)	91 (30)	
Distal to splenic flexure	85 (65)	209 (70)	0.381
Synchronous			
T-stage			
0/1/2	43 (33)	83 (27)	
3/4	87 (67)	223 (73)	0.210
N-stage[a]			
0	77 (61)	187 (64)	
1/2	49 (39)	105 (36)	0.569
Differentiation[b]			
Poor	13 (10)	29 (10)	
Moderate/well	114 (90)	273 (90)	0.840
Venous Invasion[c]			
Present	68 (55)	157 (56)	
Absent	56 (45)	121 (44)	0.761
Absolute neutrophil count[d]			
≥7.5	12 (9)	41 (15)	
<7.5	115 (91)	242 (85)	0.160
Neutrophil/lymphocyte ratio[d]			
≥ 5	20 (16)	68 (24)	
< 5	107 (84)	215 (76)	0.059

[a]n=418, [b]n=429, [c]n=402, [d]n=410

8 AN EXAMINATION OF PROGNOSTIC FACTORS IN NON SCREEN-DETECTED TNM STAGE I COLORECTAL CANCER

8.1 Introduction

Population screening for colorectal cancer using the faecal occult blood test (FOBt) has been shown to improve cancer specific mortality through the detection of early stage disease (Mandel, Bond et al. 1993; Hardcastle, Chamberlain et al. 1996; Kronborg, Fenger et al. 1996). Through this detection of early stage tumours, such screening programmes have the potential to change the entire landscape of the management and outcome of colorectal cancer. For example, studies in the pre-screening era noted that less than 20% of all patients presented with TNM Stage I disease (Nicholson, Finlay et al. 2011; Roxburgh, McTaggart et al. 2013). However, it has been shown that TNM Stage I tumours can account for approximately 50% of colorectal cancers detected through FOBt screening programmes (UK Colorectal Cancer Screening Pilot Group 2004; Logan, Patnick et al. 2012). Hence, an overall stage-shift towards early stage disease is anticipated over the next decade (McClements, Madurasinghe et al. 2012). There is evidence from our geographical area, presented in Chapter 2, that such a stage shift has already occurred.

Cancer outcome following a diagnosis of TNM Stage I colorectal cancer is very good, and an average 5-year cancer specific survival of over 90% is widely reported (Cancer Research UK). As such, adjuvant chemotherapy is not recommended in these patients (Nelson, Petrelli et al. 2001, SIGN 2011). Nevertheless, some will develop metastatic disease and ultimately succumb to their illness and others will die of alternate causes, such as cardiovascular disease. This would be increasingly relevant to those detected through screening, as while screening improves cancer specific mortality, no effect on overall survival has been shown on mature follow up (Hewitson, Glasziou et al. 2008).

Many risk factors associated with a diagnosis of colorectal cancer are similar to those for cardiovascular disease (Parkin, Olsen et al. 2009), which is the leading cause of death in individuals over the age of 50 (Office of National Statistics 2012). It is now increasingly recognised that independent of TNM Stage, there are host factors that may be of importance in predicting outcome. In particular, the presence of an elevated systemic inflammatory response (Ishizuka, Nagata et al. 2007; Park, Watt et al. 2015) as evidenced by an alteration in circulating acute phase proteins, such as C-reactive protein (CRP) and albumin (modified Glasgow Prognostic Score (mGPS)), is associated not only with poorer outcome in colorectal cancer, but more recently it has been linked to all-cause mortality in a large incidentally sampled cohort (Proctor, McMillan et al. 2015).

There is a paucity of evidence examining tumour and, in particular, host factors in determining outcome specifically in patients with TNM Stage I colorectal cancer. Because of limited follow-up, an examination of these factors solely within screen-detected disease is not yet possible. However, as discussed in Chapter 7, there appears to be few differences between screen-detected and non screen-detected TNM Stage I disease.

The aim of the present study was to examine tumour and host determinants of outcome in patients undergoing resection for TNM Stage I colorectal cancer with mature follow-up.

8.2 Materials and methods

From January 2000 to December 2008 (inclusive), all patients undergoing a resection, with pathologically confirmed TNM Stage I disease, across four hospitals in the north of Glasgow were identified. Data was collected in both a prospective (Glasgow Royal Infirmary) and retrospective (Stobhill Hospital, Western Infirmary, Gartnavel General Hospital) manner. Any patient with a synchronous cancer, inflammatory bowel disease or who had received neo-adjuvant therapy was excluded. Those with their disease managed entirely endoscopically, without formal colonic or rectal resection, were also excluded from the study.

Tumours were staged according to the conventional tumour node metastasis (TNM) classification (5^{th} Edition) (Sobin and Fleming 1997). Further details on high-risk tumour features, such as the presence of venous invasion (Roxburgh, McMillan et al. 2014), poor differentiation (Compton, Fielding et al. 2000) or those in whom less than 12 lymph nodes were examined (Compton, Fielding et al. 2000) were extracted from pathology reports. Those with inadequate information on the number of nodes examined in pathology reports were excluded from the analysis.

The mGPS was used as an estimate of the SIR as has been described previously, using pre-operative blood results taken most immediately and not more than 1 month prior to surgery (McMillan 2012). Briefly, patients with a CRP $\leq$ 10 mg/L were allocated a score of 0, a CRP >10 mg/L and albumin $\geq$ 35g/L a score of 1 and a CRP >10mg/L and albumin <35g/L a score of 2. Due to limited events during follow-up, for survival analysis the mGPS was further dichotomised into being elevated (mGPS = 1 or 2) or not elevated (mGPS = 0).

Survival was determined from both individual electronic patient records and by matching patients to the Registrar General (Scotland). Date of censor was 12th December 2014. Overall survival (OS) was the primary outcome measure and was calculated from date of surgery until date of death. Cancer specific survival (CSS) was calculated from date of surgery until date of death from recurrent or metastatic colorectal cancer. A post-operative death was defined as a death within 30 days of operation.

The study was discussed and approved by the West of Scotland Research and Ethics Committee (REC Ref: 11/AL/0382 – Molecular and cellular mechanisms underlying development and progression of colorectal cancer. September 2011)

Statistical analyses

The relationship between clinicopathological features and survival was examined using Kaplain-Meier log-rank survival analysis and univariate Cox proportional hazards regression to calculate hazard ratios (HR) and 95% confidence intervals (95% CI). Statistically significant variables on univariate analysis were then taken forward into a multivariate model using a backwards conditional method. Associations between variables were examined using the Chi-squared test. Fisher's exact test was used for assessing associations where the expected individual cell counts were less than 5. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA)

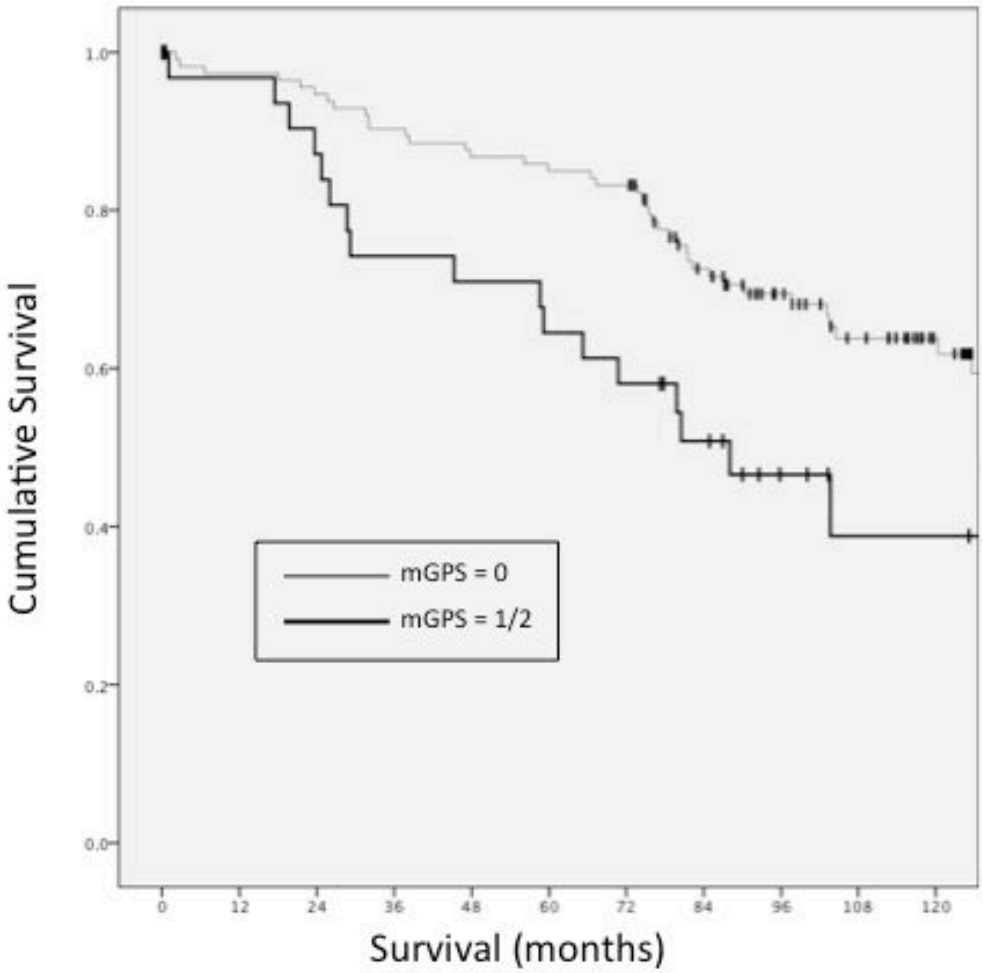
8.3 Results

A total of 191 patients were identified and included in the study. There were 105 (55%) males, 91 (48%) were over the age of 75 years and 7 (4%) patients underwent an operation as an emergency. In those with a pre-operative CRP result (n=150), 35 (24%) patients had evidence of an elevated mGPS (Table 8.1).

The median follow-up of survivors was 116 months with a minimum follow-up of 72 months. During follow-up 88 (46%) patients died of which 7 (8%) were postoperative deaths, 15 (17%) were cancer-related deaths and 66 (75%) were non cancer-related deaths. This resulted in a 5 year CSS of 95% and a 5 year OS of 76%. Excluding postoperative deaths, on univariate analysis, advancing age ($p<0.001$), emergency presentation ($p=0.008$) and an elevated mGPS ($p=0.012$) were associated with reduced OS. On multivariate analysis, only age (HR = 3.611, 95% CI:2.049 - 6.365, $p<0.001$) and the presence of an elevated mGPS (HR = 2.173, 95% CI:1.204 – 3.921, $p=0.010$) retained significance (Table 8.2, Figure 8.1).

There was an association between an elevated mGPS and emergency presentation ($p=0.040$). In view of this, survival in elective procedures was examined independently (Table 8.3). Excluding postoperative deaths, on univariate analysis, advancing age ($p<0.001$) and an elevated mGPS ($p=0.034$) were associated with reduced OS. On multivariate analysis, both age (HR = 3.503. 95% CI:1.980 – 6.196, $p<0.001$) and the presence of an elevated mGPS (HR = 2.104, 95% CI:1.155 – 3.835, $p= 0.015$) retained significance (Table 8.3). There were no further associations between the presence of an elevated mGPS and additional clinicopathological variables (Table 8.4). The unadjusted difference in mean OS between those with an elevated mGPS and those without was 31 months (Table 8.4).

Data was further stratified to assess any temporal trends that may have developed over the timeframe. Comparing patients operated on between 2001 and 2004 to those operated on between 2005 and 2008, there were no differences in age (p=0.548), sex (p=0.292), mode of presentation (p=0.345), site of tumour (p=0.149), t-stage (p=0.969), tumour differentiation (p=0.656) or the presence of an elevated mGPS (p=0.520). Patients operated on between 2001 and 2004 were more likely to have less than 12 lymph nodes examined (61% vs 44%, p=0.020) and there was a trend towards a lower venous invasion rate (17% vs 28%, p=0.073). Date of operation was not associated with OS (Tables 8.2 & 8.3).



Number at risk

mGPS = 0	114	110	107	102	98	96	89	65	51	38	28
mGPS = 1/2	33	30	27	23	22	20	17	12	7	5	4

Figure 8.1: Relationship between an elevated modified Glasgow Prognostic Score (mGPS) and overall survival (OS) in patients following resection for TNM Stage I colorectal cancer (excluding postoperative deaths)

8.4 Discussion

The results of the present study show that with mature follow-up, although cancer specific survival was 95%, overall survival was 76% in patients undergoing resection for TNM Stage I colorectal cancer. Furthermore, in these patients, the presence of an elevated SIR, as measured by the mGPS, was associated with poorer outcome. Taken together, this supports the argument that the SIR can be used as a means of identifying patients with a poorer outcome even within very early stage colorectal cancer.

The results of the present study confirm previous work that has shown that long-term oncological outcome in TNM Stage I disease is excellent (Cancer Research UK). However, a significant amount of patients will die of other causes and there is a paucity of evidence focussing on OS, which is ultimately of most relevance in patient outcome. In particular, to our knowledge, there have been no studies examining the relationship between the SIR and OS in TNM Stage I disease. Given that the SIR has been shown to be associated with adverse outcomes in both cardiovascular disease as well as cancer, it may represent a nexus from which overall survival may be predicted and improved in this patient cohort. For example, several large prospective cohort studies have identified inflammatory mediators including as CRP and albumin, as being predictive of both all cause, cancer-specific mortality and cardiovascular mortality in the over 50s (Van Hemelrijck, Eichholzer et al. 2012; Van Hemelrijck, Harari et al. 2012)

It is of interest to compare this to previous work in our geographical area that has identified that age and emergency presentation are associated with survival in TNM Stage II disease (Oliphant, Horgan et al. 2015). In the present study when adjusted for the SIR, as evidenced by mGPS, emergency presentation failed to retain prognostic significance. This is in contrast to a previous study, predominantly in TNM Stage II disease, that had shown that while emergency presentation and the SIR were linked, they both represented

independent predictors of CSS (Crozier, Leitch et al. 2009). This disparity is likely due to the focus on OS in the present study and the low number of cancer-related deaths. Furthermore, it may be speculated that within very early stage disease, emergency presentation, and its relationship with OS, represents a surrogate for a pro-inflammatory state that the mGPS more accurately recapitulates.

In addition to the long-term sequelae, there are short-term consequences of an elevated preoperative SIR that are important to consider. Colorectal resections can be associated with significant morbidity including both infective and non-infective postoperative complications. The preoperative SIR has been previously shown to be predictive of the development of a postoperative infection (Moyes, Leitch et al. 2009) and is associated with an elevated postoperative SIR, as measured by CRP (Crozier, McKee et al. 2007). Such a rise in the postoperative CRP is associated with higher rates of both surgical-site and remote infective complications (Platt, Ramanathan et al. 2012). In particular, in a recent meta-analysis the use of Day 3 CRP as a predictor of an anastomotic leak in the postoperative course at a threshold of 172 mg/l was found to have a negative predictive value of 97% (Singh, Zeng et al. 2014).

It is important to identify why individuals may have an elevated preoperative SIR in order to potentially identify a target for intervention. The SIR has been linked to a number of patient-related factors including smoking (Frohlich, Sund et al. 2003), diabetes (Dehghan, Kardys et al. 2007) and obesity (Ridker, Buring et al. 2003). In the context of colorectal cancer specifically, the SIR has been found to be associated with preoperative impaired patient physiology, however, it has been shown that it can determine outcome independent of comorbidity (Richards, Leitch et al. 2010). Therefore, to equate the SIR to a mere surrogate of comorbid disease would be to oversimplify a more complex interaction

between tumour and host. However, as a global assessment of the patient it may be that it represents a therapeutic target for potential intervention (Diakos, Charles et al. 2014).

A diagnosis of cancer has been identified as a 'teachable moment' whereby individuals are more receptive to changes in risk-related lifestyle and behaviour (McBride, Emmons et al. 2003). Indeed, the recently published BeWEL study has identified that a weight loss programme can be successfully instigated in patients who have adenomata identified at colonoscopy following a positive FOBt screening test (Anderson, Craigie et al. 2014). The authors reported that interventions including exercise not only reduced weight, but improved blood pressure and glucose metabolism markers after 1 year. The SIR was not reported on within the BeWEL study, however weight control and exercise programmes have previously been shown to reduce the SIR (Lira, Rosa Neto et al. 2014). The present study identifies a subgroup of patients that have a poorer outcome and hence may be suitable for targeting with such a programme.

In addition to lifestyle measures such as diet and exercise, there is potential to manipulate the SIR through pharmacological methods. There is evidence that both statin (Ridker, Rifai et al. 1999; Ridker, Rifai et al. 2001) and aspirin (Ridker, Cushman et al. 1997) use can reduce circulating CRP levels and this can have a positive effect on outcomes from cardiovascular disease (Ridker, Buring et al. 2003). Furthermore, these medications have also been shown to have a potential role in the prevention of colorectal cancer development (Flossmann and Rothwell 2007; Bardou, Barkun et al. 2010) and progression (Rothwell, Fowkes et al. 2011). The argument for a 'polypill', combining blood pressure and cholesterol lowering medication as well as antiplatelet treatments, has previously been made to reduce deaths from cardiovascular disease (Wald and Law 2003) however its benefits remain uncertain when used in a relatively unselected patient population (de Cates, Farr et al. 2014). Prospective studies are required to assess whether these medication

should be routinely recommended in inflamed patients with early stage colorectal cancer due to these combined effects of cardiovascular protection and chemoprevention.

The strengths of the present study include the relatively large numbers with long-term follow-up. In addition, the present study has included detailed high-risk tumour factors such as the presence of venous invasion. The main limitation of the study is that this is a historic cohort captured over a prolonged timeframe. As such, temporal changes in staging and management may have taken place. Indeed, the proportion of patients with less than 12 nodes examined was lower in those operated on in earlier years. Such a problem is inherent when examining early stage disease that was uncommon prior to the introduction of screening. However, this has been adjusted for within survival analysis and it is reassuring that date of operation was not associated with OS in this cohort.

Within the pathological reporting of specimens there were a large number of patients who had suboptimal lymph node examination and hence may be perceived as being understaged. The present study has shown this to be associated with historic changes in processing of specimens. In addition, it may also be due to the relatively high proportion of rectal tumours in this cohort. However, if this were to have introduced bias of understaging then it would be expected that outcomes would be poorer in this group, which was not the case. Finally, a perceived limitation may be the lack of cancer specific survival analysis within the present study. However, due to the small proportion of cancer deaths in this cohort, such analysis is problematic. Also, the relevance of CSS to the individual patient is limited and, particularly in the screened population, recommendations for reporting effects on OS have been made (Penston 2011).

In summary, patients undergoing resection for TNM Stage I colorectal cancer have an excellent oncological outcome, however only around three quarters are alive at 5 years. The presence of an elevated preoperative SIR, as measured by the mGPS, is an

independent marker that identifies patients with poorer overall survival and potentially identifies a subgroup that may benefit from targeted intervention.

Table 8.1: Baseline characteristics of patients undergoing resection for TNM Stage I colorectal cancer

	All patients n(%)
	191
Age	
<75	100 (52)
≥75	91 (48)
Sex	
Female	86 (45)
Male	105 (55)
Mode of presentation	
Emergency	7 (4)
Elective	184 (96)
Tumour Site	
Colon	122 (64)
Rectum	69 (36)
T-stage	
1	54 (28)
2	137 (72)
Venous invasion[a]	
Present	37 (22)
Absent	130 (78)
Differentiation	
Poor	3 (2)
Moderate/well	188 (98)
Less than 12 lymph nodes	
Yes	102 (53)
No	89 (47)
mGPS[b]	
0	115 (77)
1	22 (15)
2	13 (9)
Date of operation	
2001 - 2004	103 (54)
2005 - 2008	88 (46)
Outcome at date of censor	
Alive	103 (54)
Postoperative death	7 (4)
Cancer-related death	15 (8)
Non cancer-related death	66 (35)

[a] data complete 167 (87%) patients
[b] mGPS = modified Glasgow Prognostic Score. Data complete 150 (79%) patients

Table 8.2: Factors associated with overall survival following resection for TNM Stage I colorectal cancer (excluding post operative deaths)

	Univariate survival analysis HR (95% C.I.)	p-value	Multivariate survival analysis HR (95% C.I.)	p-value
Age *(<75 / ≥75)*	**3.722** **(2.310 – 5.996)**	**<0.001**	**3.611** **(2.049 – 6.365)**	**<0.001**
Sex *(Female / Male)*	0.895 (0.579 – 1.385)	0.620	-	
Mode of presentation *(Elective / Emergency)*	**3.443** **(1.387 – 8.543)**	**0.008**	1.036 (0.240 – 4.469)	0.962
Tumour Site *(Colon / Rectum)*	0.915 (0.580 – 1.442)		-	
T-stage *(1 / 2)*	1.104 (0.676 – 1.804)	0.692	-	
Venous invasion *(No / Yes)*	1.304 (0.762 – 2.229)	0.333	-	
Differentiation *(moderate-well / poor)*	1.661 (0.407 – 6.778)	0.479	-	
Less than 12 lymph nodes *(No / Yes)*	1.122 (0.721 – 1.745)	0.610	-	
mGPS *(0 / 1+2)*	**2.076** **(1.172 – 3.677)**	**0.012**	**2.173** **(1.204 – 3.921)**	**0.010**
Date of operation *(2001-2004 / 2005 – 2008)*	1.233 (0.769 – 1.976)	0.385	-	

Table 8.3: Factors associated with overall survival following resection for TNM Stage I colorectal cancer (excluding emergency presentation and post operative deaths)

	Univariate survival analysis	p-value	Multivariate survival analysis	p-value
	HR (95% C.I.)		HR (95% C.I.)	
Age *(<75 / ≥75)*	**3.634 (2.228 – 5.926)**	**<0.001**	**3.503 (1.980 – 6.196)**	**<0.001**
Sex *(Female / Male)*	0.832 (0.530 – 1.305)	0.423	-	
Tumour Site *(Colon / Rectum)*	0.939 (0.589 – 1.498)	0.791	-	
T-stage *(1 / 2)*	1.042 (0.634 – 1.713)	0.871	-	
Venous invasion *(No / Yes)*	1.343 (0.772 – 2.336)	0.297	-	
Differentiation *(moderate-well / poor)*	1.745 (0.427 – 7.130)	0.438	-	
Less than 12 lymph nodes *(No / Yes)*	1.041 (0.661 – 1.641)	0.861	-	
mGPS *(0 / 1+2)*	**1.908 (1.050 – 3.467)**	**0.034**	**2.104 (1.155 – 3.835)**	**0.015**
Date of operation *(2001-2004 / 2005 – 2008)*	1.229 (0.753 – 2.004)	0.410	-	

Table 8.4: Relationship between clinicopathological factors, overall survival (OS) and the modified Glasgow Prognostic Score (mGPS) in patients undergoing resection for TNM Stage I colorectal cancer

	mGPS		
	0 n(%)	1/2 n(%)	p-value
	115	35	
Age			
<75	65 (56)	17 (49)	
≥75	50 (44)	18 (51)	0.410
Sex			
Female	49 (43)	16 (46)	
Male	66 (57)	19 (54)	0.746
Mode of presentation			
Emergency	1 (1)	3 (9)	
Elective	114 (99)	32 (91)	0.040
Tumour Site			
Colon	69 (60)	25 (71)	
Rectum	46 (40)	10 (29)	0.223
T-stage			
1	37 (32)	6 (17)	
2	78 (68)	29 (83)	0.086
Venous invasion[a]			
Present	28 (27)	6 (19)	
Absent	75 (73)	25 (81)	0.382
Differentiation			
Poor	3 (3)	0	
Moderate/well	112 (97)	35 (100)	0.448
Less than 12 lymph nodes			
Yes	60 (52)	19 (54)	
No	55 (48)	16 (46)	0.827
Date of operation			
2001 – 2004	52 (45)	18 (51)	
2005 – 2008	63 (55)	17 (49)	0.520
Mean OS			
(months (95% CI))	122 (112 – 131)	91 (71 – 110)	0.010

[a] n= 134 (89%)

9 THE INTERRELATIONSHIPS BETWEEN TUMOUR AND HOST CLINICOPATHOLOGICAL CHARACTERISTICS IN SCREEN-DETECTED T1/2 COLORECTAL CANCER

9.1 Introduction

It is increasingly recognised that in addition to stage at diagnosis there are a variety of tumour and host factors that can affect an individuals' outcome following a diagnosis of colorectal cancer. There are certain pathological characteristics of the tumour itself that are recognised to be indicative of phenotypically more aggressive disease. These include the presence of venous invasion, lymphatic invasion and perineural invasion (Pathologists 2014). For example, in a previous landmark paper, the presence of any of these three features (collectively referred to as VELIPI) was suggested to be representative of early metastatic spread and was predictive of disease free survival in colorectal cancer (Pages, Berger et al. 2005).

Also, the immune response at the tumour/host interface has been shown to be of prognostic significance, with over 40 published studies confirming that a pronounced local inflammatory cell infiltrate in or around the tumour is associated with an improved outcome (Roxburgh and McMillan 2012). Recently, an automated method of scoring the peri-tumoural inflammatory infiltrate has been proposed as a method of standardising reporting (Forrest, Guthrie et al. 2014). However, all previous work has focussed mainly on TNM Stage II and III disease, as this has been representative of the stage of disease most commonly encountered and our understanding of the role of the peri-tumoural local inflammatory response in early stage disease is poor.

Recently, the development of colorectal cancer screening programmes has led to an increase in the proportion of early stage tumours being detected (Logan, Patnick et al.

2012). This has led to a stage shift amongst non-metastatic disease to higher numbers of early stage disease being commonly encountered in clinical practice (Chapter 2). Overall, patients with these early stage tumours have an excellent cancer specific outcome and the majority of patients who undergo a curative resection ultimately die of something else (Chapter 8). However, an examination of these tumours aids our understanding of the natural history of colorectal, in particular when and how certain high-risk characteristics develop.

The aim of the present study was to examine the interrelationships between tumour and host clincopathological characteristics in screen-detected T1/2 colorectal cancer.

9.2 Materials and methods

Derivation of cohort

From the original extract of data from the first round of FOBt screening in NHS GG&C, as described in Chapter 3, details were available for a total of 398 patients with screen-detected colorectal cancer. Of those, 370 patients underwent procedures with a curative intent. Excluding those who had undergone neoadjuvant therapy (n=31) or had T3/4 disease (n= 157) identified a cohort of 181 patients in whom slides were retrieved from archive (1 patient; unable to retrieve). Following review by a consultant pathologist a further 13 were excluded (11 patients - debate as to whether true invasive cancer rather borderline high grade dysplasia present; 2 patients - fragmented endoscopic biopsies only). Of the 167 patients remaining, 119 patients underwent formal resection following which 78 patients were included for final analysis with evidence of residual mural tumour on the resected specimen (Figure 9.1). Patients in whom no residual tumour on resection was seen or who were treated with endoscopic resection only were excluded due to the lack of an appropriate margin for scoring of the local inflammatory response.

Data collection

Tumours were staged according to the conventional tumour node metastasis (TNM) classification (5th Edition)(Sobin and Fleming 1997). Additional high-risk tumour features such as the presence of venous invasion, perineural invasion and lymphatic invasion were identified from pathology reports. A patient was termed VELIPI positive if at least one of these features (including nodal involvement as evidence of lymphatic invasion) was present.

Both the absolute neutrophil count and the neutrophil to lymphocyte ratio (NLR) were used as a markers of the pre-operative systemic inflammatory response (SIR) and were obtained from pre-operative blood results taken most immediately and not more than 6

weeks prior to surgery. With regards the NLR, a previously validated threshold of ≥5 was used as being evidence of a significantly elevated SIR (Walsh, Cook et al. 2005). An absolute neutrophil level greater than 7.5 x 10^9 was defined as elevated as per local laboratory guidelines.

The local peri-tumoural inflammatory response was calculated from routine haematoxylin and eosin-stained (H&E) slides using both the visual Klintrup-Makinen (K-M) criteria (Klintrup, Makinen et al. 2005) and the automated inflammatory cell density (Forrest, Guthrie et al. 2014) as has previously been described. At least 1 H&E slide (range 1-3) was scanned using a high resolution digital scanner (Hamamatsu NanoZoomer, Hamamatsu, Welwyn Garden City) and images viewed and assessed using Slidepath Digital Image Hub and Image Analysis module (Leica Microsystems, Wetzlar, Germany).

The visual K-M score uses a 4-point scale to assess the degree of inflammation at the invasive margin of the tumour. Briefly explained, a score of 0 indicates no increase in inflammatory cells, a score of 1 represented mild or patchy increase, 2 a prominent reaction and 3 a florid 'cup-like' reaction. This was further dichotomised to a visual K-M grade of weak (score 0 to 1) or strong (score 2 to 3) inflammation in line with previous studies (Roxburgh and McMillan 2012). A mean score and grade was created for each patient dependent based on individual slide scores. To assess for concordance two investigators assessed 40 patients (r=0.490), after retraining (r=0.892). The local inflammatory reaction in the remaining patients was then assessed by a single observer.

The automated inflammatory cell density utilises the 'Measured stained cells algorithm' in the Image Analysis module of Slidepath as has been described previously using the rectangular box method (Forrest, Guthrie et al. 2014). This algorithm has previously been optimised to count only inflammatory cells and exclude other cell types including tumour cells. In order to guide the software to the invasive margin this was manually selected. The

area of maximal tumour depth was identified visually and then, at a magnification of 20x, three rectangular boxes were drawn along the margin (Figure 9.2). The algorithm was then run and the density of inflammatory cells was calculated and output expressed as positive cells/mm^2. The mean score of the three boxes and subsequently the mean score of all slides for each tumour specimen was then calculated.

Ethical approval for the study was obtained from the West of Scotland Ethics Committee (REC ref 12/WS/0152 - An investigation into tumour and host prognostic factors in early stage colorectal cancer and their correlation with clinical outcome. June 2012).

Statistical analysis

Associations between categorical variables were examined using χ^2 tests for linear trend unless otherwise specified. All variable were grouped according to standard or previous published thresholds. To compare inflammatory cell density, nonparametric analysis was performed. For data with two categories the Mann Whitney U test was used and in those with more than two categories an analysis of variance using the Kruskal-Wallis test was performed. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA)

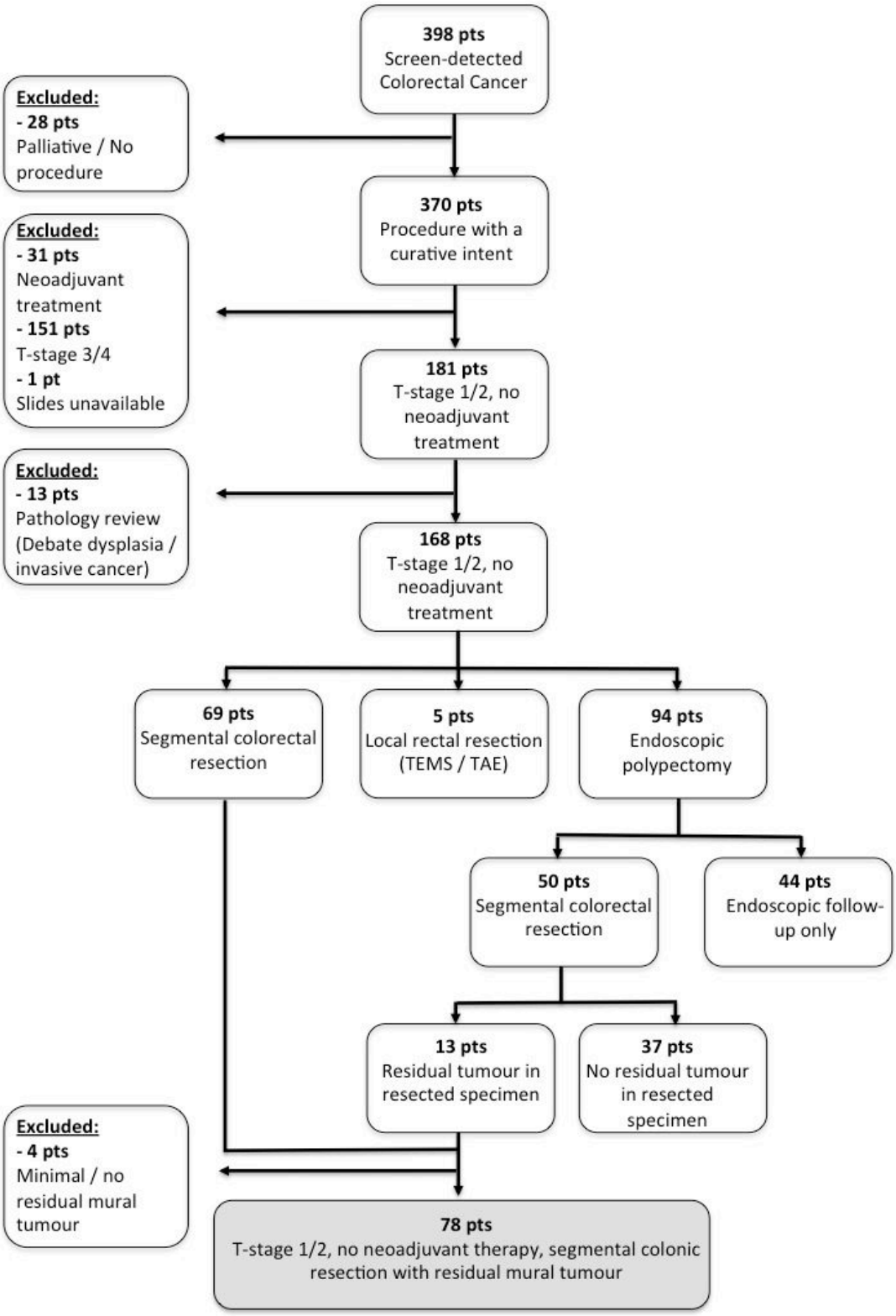


Figure 9.1: Derivation of cohort of patients with screen-detected T1/2 colorectal cancer for assessment of the local inflammatory response

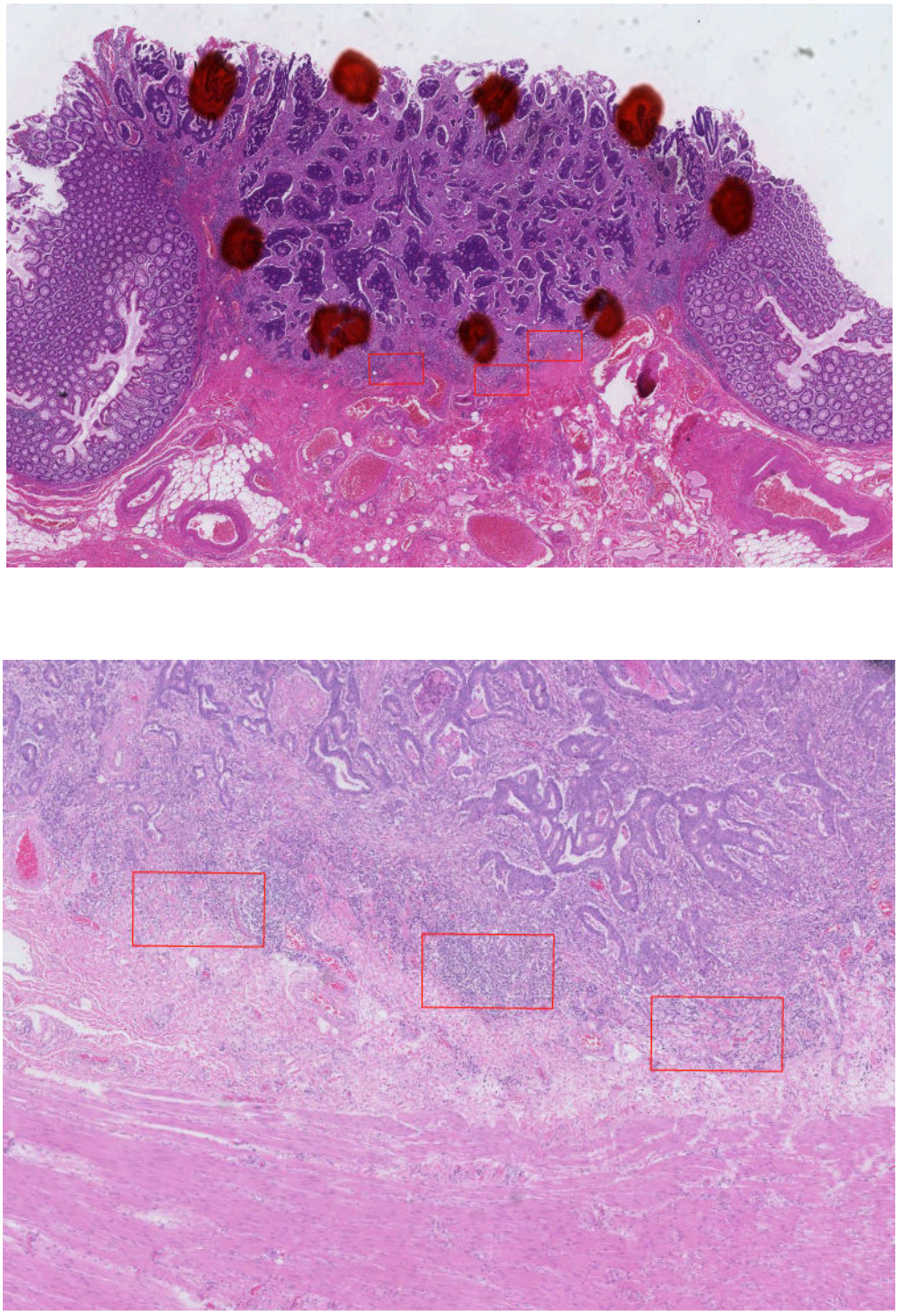


Figure 9.2: Representative examples of rectangular boxes at the invasive margin used for the automated inflammatory cell density

(note red ink dots in upper most picture used to identify tumour for alternative study)

9.3 Results

A total of 78 patients with screen-detected T1/2 disease with evidence of residual mural tumour having undergone a formal resection were included. There were 56 (72%) males, the majority were deprived (52% most deprived two quintiles of deprivation) and 8 (10%) were taking aspirin. The majority of tumours were rectal (72%). Venous invasion and lymphatic involvement (including nodal disease) was present in 27% and 22% of patients respectively. There was no documented evidence of perineural invasion. Therefore, 30 (39%) patients were VELIPI positive. Only 6% of patients had evidence of an elevated SIR as measured by either a raised neutrophil count or an elevated NLR.

Using the visual K-M score, 33 (42%) patients had scores of 2 and 3 and were therefore graded as having evidence of a strong peri-tumoural inflammatory infiltrate. The association between the visual K-M score and grade, and the automated inflammatory cell density was then examined (Table 9.1, Figure 9.2). There were significant differences between the automated inflammatory cell density and both the visual K-M grade (p=0.001) and the visual K-M scores 2 and 3 (p=0.040). There was a trend for a difference between visual K-M scores 1 and 2 (p=0.059).

The association between tumour and host features was then examined with regard to T-stage (Table 9.2). There was an association between more advanced T-stage and increased lymphatic involvement (including nodal disease) (9% vs 31%, p=0.020). There was no difference in venous invasion rates (24% vs 29%, p=0.648) and the local inflammatory response as measured by either the visual K-M grade (p=0.630) or the automated inflammatory cell density (p=0.975).

The interrelationships of tumour and host features were then examined both within the whole cohort and also in those with T1 disease only (Tables 9.3a & Table 9.3b). There was

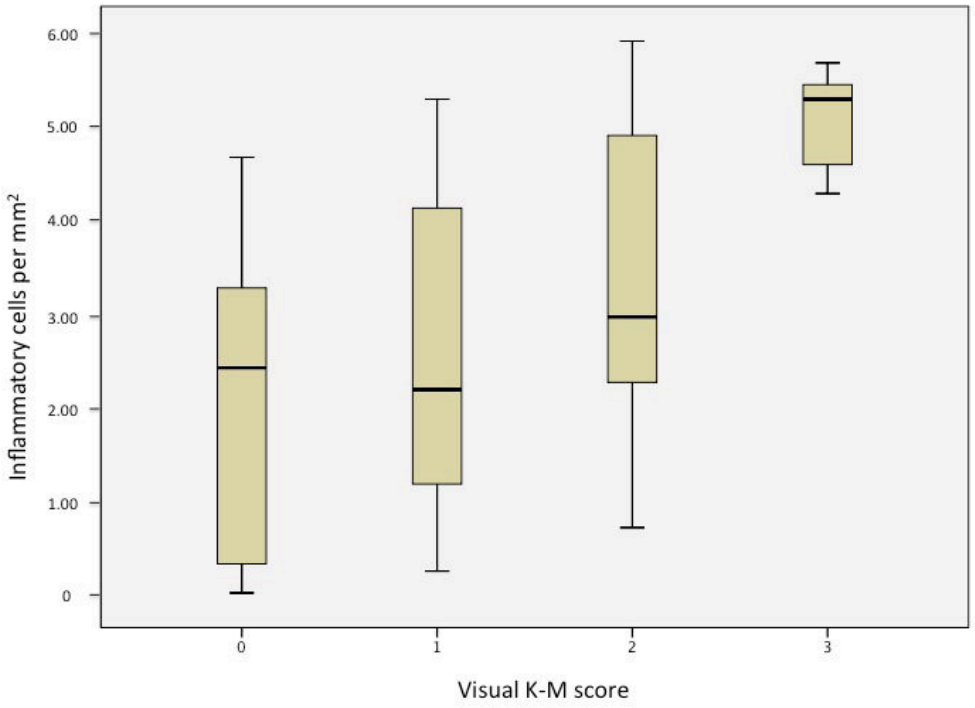
no evidence of a link between the inflammatory cell infiltrate, measured with the either the visual K-M grade or automated inflammatory cell density, and tumour and host factors included for analysis.

Table 9.1: Association between automated inflammatory cell density, visual K-M score and visual K-M grade in patients with T1/2 colorectal cancer undergoing resection

	Inflammatory cells per mm^2 median (range)	p-value
visual K-M score		
0	2.53 (0.02 – 4.07)	
1	2.45 (0.21 – 5.05)	0.257 [a]
2	2.90 (0.74 – 6.01)	0.059 [b]
3	4.97 (3.82 – 5.55)	0.040 [c]
visual K-M grade		
Weak	2.34 (0.02 – 5.05)	
Strong	3.53 (0.74 – 6.01)	0.001

[a] visual K-M 0 versus 1, [b] visual K-M 1 versus 2, [c] visual K-M 2 versus 3

(a)



(b)

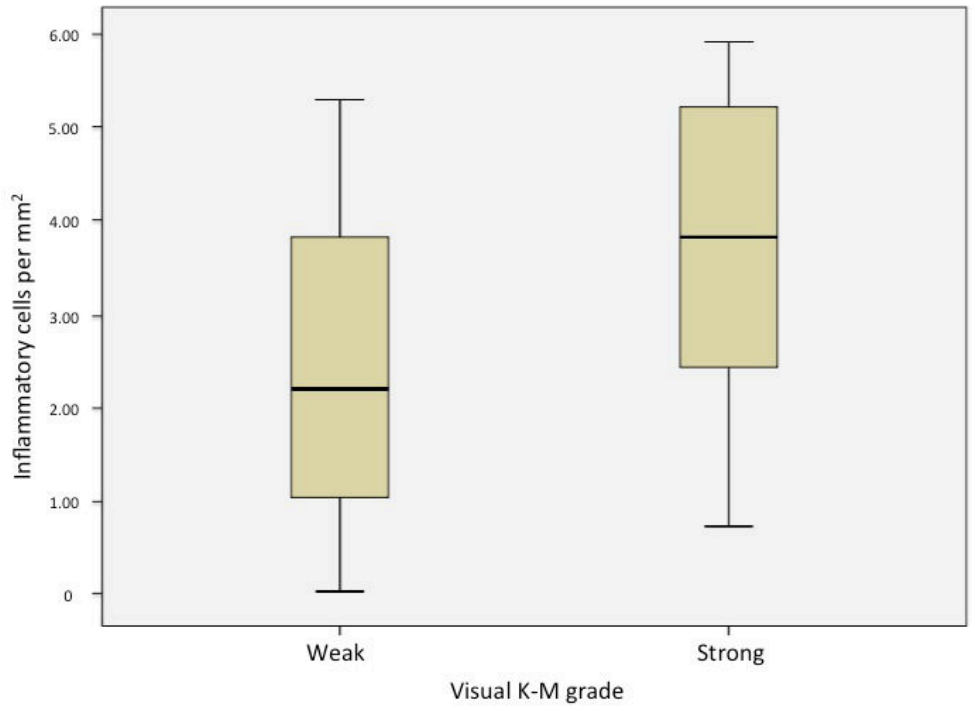


Figure 9.3: Comparison between automated inflammatory cell density, visual K-M score (a) and visual K-M grade (b)

9.4 Discussion

The results of the present study have validated the use of an existing automated tool in assessing the local peri-tumoural inflammatory response within early stage T1/2 colorectal cancer. In addition, it has shown that the lymphatic involvement rate is lower in T1 compared to T2 disease, however, venous invasion rates and the local inflammatory response are unchanged. This suggests that venous invasion and a pronounced local inflammatory response, are features that occur early in tumour development and may represent potential therapeutic targets for the future.

The peri-tumoural inflammatory response has been assessed in a large number of studies over the past 40 years and has consistently been shown to be associated with better outcome (Roxburgh and McMillan 2012). In addition, the lack of an inflammatory infiltrate and the presence of a high tumour associated stroma percentage have been shown to be associated with a poorer outcome (Park, Richards et al. 2014). The mechanism behind such a local reaction at the host-tumour interface is as yet not fully understood however may involve a process called epithelial-mesenchymal transition (EMT). EMT is a process whereby epithelial cells lose cell-to-cell contact and develop migratory and invasive properties, and is a normal physiological process involved in tissue growth and repair (Bates and Mercurio 2005). It has been proposed that a loss of inflammatory infiltrate facilitates stroma formation that in turn leads to tumour growth and invasion (Park, McMillan et al. 2015).

Within the present study, a pronounced local inflammatory reaction was not significantly associated with adverse tumour features such as venous invasion or lymphatic invasion. This was perhaps surprising as previous work in more advanced disease has suggested that this might be the case (Forrest, Guthrie et al. 2014). However, it is important to consider that early stage disease represents a relatively homogenous group with excellent cancer-

specific outcome. It is likely therefore, that the local inflammatory response develops more significance as the disease progresses. Understanding this mechanism is crucial to both our understanding of why early stage disease progresses and also where potential immunomodulatory targets may be identified.

It is necessary to put the present study into context with regards patient outcome. It has previously been proposed that the combination of T-stage and venous invasion is superior to nodal status in determining cancer specific outcome in T1/2 disease (Roxburgh, McMillan et al. 2014). Hence, all T1/2 tumours and not just those that were node-negative were included in the present study. Despite a minimal follow-up of 3 years, only 4 (5%) patients died, none of cancer (2 post operative deaths, 2 non-cancer related deaths – data not presented). Therefore, survival analysis was not undertaken. Larger cohorts with mature follow-up, such as used in Chapter 8 are required to assess whether the local inflammatory response remains a valid prognostic factor in early stage screen-detected disease.

In order to ensure an assessment of the local inflammatory response is routinely adopted in clinical practice a practical, reliable and reproducible method of assessment is required. The present study utilises routine H&E slides and readily available digital imaging software to perform the analysis. It was reassuring to note that assessment of the local inflammatory infiltrate using the visual K-M was accurately measured using the automated inflammatory cell density within T1/2 disease. This has implications for further projects examining this in larger numbers and validates previous work (Forrest, Guthrie et al. 2014).

The strengths of the present study are the high quality dataset and use of two validated methods in examining the host inflammatory response. In particular, the automated inflammatory cell density provides a reproducible quantitative method of examining

immune cell infiltrate. Also, the venous invasion rate in the present study was strong when compared to other studies in early stage cohorts due to the routine use of an elastin stain employed in this geographical area over this timeframe (Roxburgh, McMillan et al. 2010). This is a real strength of pathology reporting in our geographical area. For example, a recent study examining polyp cancers within Scotland, noted a venous invasion rate of 28% in the West of Scotland, compared to 12% in the rest of the country (Scottish Screen-detected Polyp Cancer Study, data unpublished).

The reporting of other high-risk characteristics such as lymphatic invasion, outside of those with nodal involvement, and perineural invasion was poor. Particularly perineural invasion, where no evidence of its presence was recorded. This reflects current RCPath audit standards where venous invasion is a core-dataset item and the other two factors are not (RCPath 2014). The use of specific stains for lymphatic invasion to improve reporting have been proposed however are not yet in use in routine clinical practice (van Wyk, Roxburgh et al. 2014). In addition, there are further stains for optimising perineural detection available (Shimada, Kido et al. 2014) and it has been noted that repeated examination of slides will increase detection (van Wyk, Roxburgh et al. 2014). Use of such techniques would increase overall detection and impact the VELIPI rate. Therefore, it may impact on any potential relationships between VELIPI and the local peri-tumoural inflammatory response. It would be of benefit to repeat such a study using these additional stains to assess whether relationships differed.

The main weakness of the present study was the difficulty in including patients for analysis. The visual K-M is not applicable to those who undergo polypectomy only or in those who have no residual tumour on their resection specimen, due to a lack of an invasive margin to assess. This accounted for over half of the patients initially selected for the study. However, to our knowledge, there is currently no validated method of assessing

intra-tumoural inflammatory cell infiltrate on routine H&E slides. Further studies should focus on either developing such a method or utilising immunohistochemistry to ensure all patients with T1/2 disease can be included. This is of increasing relevance with advances in endoscopic management that have led to a large number of patients with T1/2 disease avoiding resectional surgery (Williams, Pullan et al. 2013).

In conclusion, the present study has validated the use of an automated tool in examining the peri-tumoural inflammatory cell infiltrate in patients undergoing a resection for T1/2 screen-detected colorectal cancer. It has demonstrated that lymphatic involvement is higher in T1 compared to T2 disease, however, venous invasion rates and the local inflammatory response are unchanged. This suggests that venous invasion and a pronounced local inflammatory response, are features that occur early in tumour development. Such findings enhance our understanding of the relationship between tumour and host within early stage disease.

Table 9.2: The relationship between T-stage and tumour and host factors in screen-detected T1/2 colorectal cancer

	T-stage		
	T1 n(%) 33	**T2** n(%) 45	**p-value**
Age (years)			
≤61 / 61 – 70 / ≥ 70	17(52) / 10(30) / 6(18)	13(29) / 15(33) / 17(38)	0.079
Sex			
Female / Male	9(27) / 24(73)	13(29) / 32(71)	0.875
Deprivation (quintile)			
1-2 (most) / 3-5 (least)	21(64) / 12(36)	16(36) / 29(64)	0.014
Aspirin usage			
No / Yes	31(94) / 2(6)	39(87) / 6(13)	0.296
Site			
Colon / Rectal	20(61) / 13(39)	36(80) / 9(20)	0.060
N-stage			
0 / 1 / 2	30(91) / 2(6) / 1(3)	32(71) 10(22) / 3(7)	0.097
Tumour differentiation			
Mod/well / Poor	32(97) / 1(3)	45(100) / 0(0)	
Venous invasion			
Absent / Present	25(76) / 8(24)	32(71) / 13(29)	0.648
Lymphatic involvement (inc nodal)			
Absent / Present	30(91) / 3(9)	31(69) / 14(31)	0.020
Perineural invasion			
Absent / Present	33(100) / 0(0)	45(45) / 0(0)	
VELIPI			
Absent / Present	24(73) / 9(27)	24(53) / 21(47)	0.082
Absolute neutrophil count			
≤ 7.5> / 7.5	33(100) / 0(0)	44(98) / 1(2)	
Neutrophil/lymphocyte ratio			
< 5 / ≥ 5	31(94) / 2(6)	42(93) / 3(7)	
Visual K-M grade			
Weak / strong	15(45) / 18(55)	18(40) / 27(60)	0.630
Automated inflammatory cell density (cells per mm^2)			
Median (range)	2.70(0.02 – 5.90)	2.95(0.21 – 6.01)	0.975[a]

[a] Mann Whitney test

Table 9.3a: Interrelationships between tumour and host factors in screen-detected T1/2 colorectal cancer

	Sex	Deprivation	Aspirin usage	Site	T-Stage	N-stage	Venous invasion	Lymphatic involvement (inc nodal)	VELIPI	Visual K-M grade	Automated inflammatory cell density[a]
Age	0.746	0.174	0.007	0.876	0.079	0.497	0.592	0.459	0.689	0.782	0.632
Sex		0.469	0.148	0.657	0.875	0.530	0.275	0.463	0.811	0.170	0.385
Deprivation			0.552	0.073	0.014	0.568	0.984	0.559	0.566	0.764	0.819
Aspirin usage				0.297	0.296	0.303	0.476	0.501	0.953	0.296	0.987
Site					0.060	0.404	0.275	0.274	0.203	0.170	0.813
T-Stage						0.097	0.648	0.020	0.082	0.630	0.975
N-stage							0.223	<0.001	<0.001	0.675	0.363
Venous invasion								0.034	<0.001	0.136	0.828
Lymphatic involvement (inc nodal)									<0.001	0.915	0.759
VELIPI										0.744	0.707
Visual K-M grade											<0.001

[a] Mann Whitney /Kruskal Wallis test

Table 9.3b: Interrelationships between tumour and host factors in screen-detected T1 colorectal cancer

	Sex	Deprivation	Aspirin usage	Site	N-stage	Venous invasion	Lymphatic involvement (inc nodal)	VELIPI	Visual K-M grade	Automated inflammatory cell density[a]
Age	0.812	0.554	0.279	0.481	0.540	0.058	0.119	0.012	0.143	0.165
Sex		0.301	0.372	0.245	0.181	0.281	0.108	0.690	0.475	0.983
Deprivation			0.270	0.590	0.390	0.939	0.170	0.825	0.741	0.408
Aspirin usage				0.751	0.899	0.409	0.645	0.372	0.183	0.226
Site					0.342	0.074	0.143	0.042	0.135	0.223
N-stage						0.126	<0.001	0.012	0.193	0.245
Venous invasion							0.072	<0.001	0.604	0.334
Lymphatic involvement (inc nodal)								0.003	0.439	0.317
VELIPI									0.943	0.363
Visual K-M grade										0.004

[a] Mann Whitney /Kruskal Wallis test

10 THE INFLAMMATORY MICROENVIRONMENT IN SCREEN-DETECTED PREMALIGANT ADENOMATOUS POLYPS

10.1 Introduction

Screening for colorectal cancer with the guaiac-based faecal occult blood test (gFOBt) has been shown to reduce cancer specific mortality through the detection of early stage disease (Mandel, Bond et al. 1993; Hardcastle, Chamberlain et al. 1996; Kronborg, Fenger et al. 1996). However, as identified in Chapter 3, the majority of individuals who attend for colonoscopy following a positive screening test do not have cancer detected and a large proportion have adenomatous polyps. There is good evidence that colorectal cancer develops through the adenoma-carcinoma sequence and it has been estimated that approximately 25% of polyps greater than 1cm will develop into cancer over 20 years (Stryker, Wolff et al. 1987). There is some evidence from gFOBt screening that in the context of a high positivity rate the incidence of cancer in a given population can be reduced by removal of these polyps (Mandel, Church et al. 2000).

However, identifying which patients with polyps have a higher propensity for malignant transformation is currently poorly understood. Current guidelines advise repeat colonoscopies at 1, 3 or 5 years depending on the number, size and grade of polyp detected at index procedure. With those with multiple polyps, greater than 1cm and high-grade changes being subjected to repeated examinations at sooner intervals (Cairns, Scholefield et al. 2010). Nevertheless, there is limited evidence that this impacts on patient outcome and a recent population study has suggested that colorectal cancer mortality may actually be higher in those patients who have a high risk polyp removed compared with the general population (Loberg, Kalager et al. 2014). It is therefore imperative that a further investigation of the natural history and progression of adenomatous polyps is undertaken.

There is now a wealth of evidence that progression and outcome of colorectal cancer is related to a complex interaction between tumour and host (Hanahan and Weinberg 2011). In particular, those with a more pronounced peri-tumoural inflammatory reaction have better cancer specific outcomes (Roxburgh and McMillan 2012). However, it is not clear whether such a relationship is relevant to malignant adenomatous polyps. Previous studies examining this phenomenon have been limited by both numbers and a focus on early invasive cancer and have failed to exam the host inflammatory response across the spectrum of dysplasia and therefore our understanding of the natural history of such polyps is limited (Cui, Yuan et al. 2009; McLean, Murray et al. 2011; Cui, Shi et al. 2012).

The aim of the present chapter was to assess the role of the local inflammatory response in screen-detected dysplastic adenomas and to assess whether the type and intensity of inflammatory infiltrate differs between high-grade and low-grade dysplasia.

10.2 Materials and methods

A database of all patients with adenomas detected through the first round of the Scottish Bowel Screening Programme (SBoSP) in NHS GG&C (April 2009 to April 2011) had previously been created. The screening algorithm and derivation of this cohort has been discussed previously (Chapter 3). All colonoscopists have to comply with strict quality control measures as assessed by the Joint Advisory Group (JAG) accreditation, all polyps identified are removed at colonscopy.

A representative sample of 207 polyps from 134 individuals was chosen for inclusion in the study. All samples were processed in a single pathology department (Glasgow Royal Infirmary). All polyps were greater than 10mm in size. Details on site and macroscopic morphological appearance of the polyp were obtained from endoscopic reports. Details on post-fixation size, grade of dysplasia and microscopic appearance were obtained from pathology reports. Patient details included age, sex, and socioeconomic deprivation status. The Scottish Index of Multiple Deprivation (2009) was used as a measure of deprivation as has been described previously (SIMD 2009). Details on patient usage of Aspirin was obtained from pre-assessment documentation. Follow-up details on any further colonoscopies and details of recurrent or metachronous neoplasia (colorectal cancer or dysplastic polyp), were obtained from patients medical records on a case-by-case basis.

Ethical approval for use of this tissue was obtained from the West of Scotland Research Ethics Committee (12/WS/0152 – An investigation into tumour and host prognostic factors in early stage colorectal cancer and their correlation with clinical outcome. June 2012. Amendment approved December 2012).

Immunohistochemistry

Assessment of inflammatory cell phenotype infiltrate was carried out by immunohistochemistry. Representative archival formalin fixed paraffin embedded tissue blocks were retrieved from archive and 2.5μm sections cut. Sections were then dewaxed rehydrated through graded alcohol. An autostainer (ThermoFisher, Autostainer 480s) was used to perform staining. Antigen retrieval was carried out in a PT module (ThermoFisher) using ThermoFisher dewax/retrieve solution pH9. Primary antibody was applied for 20 minutes at RT following antigen retrieval. Signal was amplified and visualised using the ThermoFisher Quanto kit and the diaminobenzidine (DAB) colour developer. Cell surface antigens were evaluated for T-lymphocytes (CD3+) dilution 1:300 (ThermoFisher), cytotoxic T-lymphocytes (CD8+) dilution 1:100 (ThermoFisher), helper T-lymphocytes (CD45+) dilution 1:500 (ThermoFisher) and macrophages (CD68+) dilution 1:5000 (ThermoFisher).

Assessment of inflammatory infiltrate

All stained slides were converted to electronic format using a high resolution digital scanner (Hamamatsu NanoZoomer, Hamamatsu, Welwyn Garden City) and images viewed and assessed using Slidepath Digital Image Hub and Image Analysis module (Leica Microsystems, Wetzlar, Germany). The whole slide was then analysed in a semi-quantitative manner to assess intra-epithelial cell infiltrate at a resolution of 20x. Immune-cell infiltrate was graded on a four-point scale as absent, weak, moderate or strong (Figures 10.1 to 10.4). Following initial scoring, this was further dichotomised into low and high for the purpose of analysis. A total of 30 slides for each stain were scored independently by two observers to confirm consistency of scoring. The remainder of the slides were then scored by a single observer. The inter-observer intraclass coefficents for each subtype

were: CD3+ 0.66, CD8+ 0.66, CD45+ 0.29 (0.69 following retraining) and CD68+ 0.79. A kappa value above 0.6 indicates good concordance.

The total inflammatory infiltrate was then derived for each polyp based on a combination of lymphocyte (CD3+) and macrophage (CD68+) scores. For example a polyp with CD3+ High and CD68+ High had a high total inflammatory infiltrate and a polyp with CD3+ Low and CD68+ Low had a low total inflammatory infiltrate. All others had a medium total inflammatory infiltrate.

Statistical Methods

Associations between categorical variables were examined using the χ^2 test. For ordered variables with multiple categories the χ^2 test for linear trend was used. Wilcoxon signed-rank test was used for analysis of paired variables. Binary logistic regression analysis was used to assess risk of neoplasia recurrence. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA)

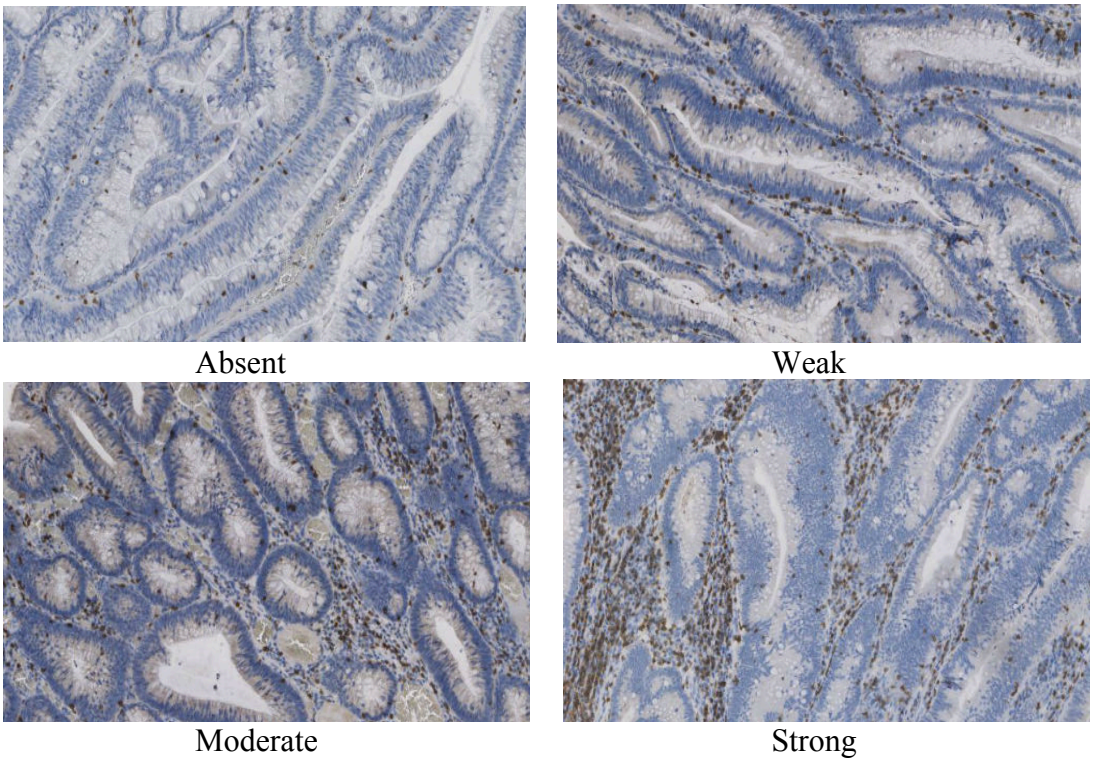


Figure 10.1a: Assessment of CD3+ T-lymphocyte inflammatory cell infiltrate

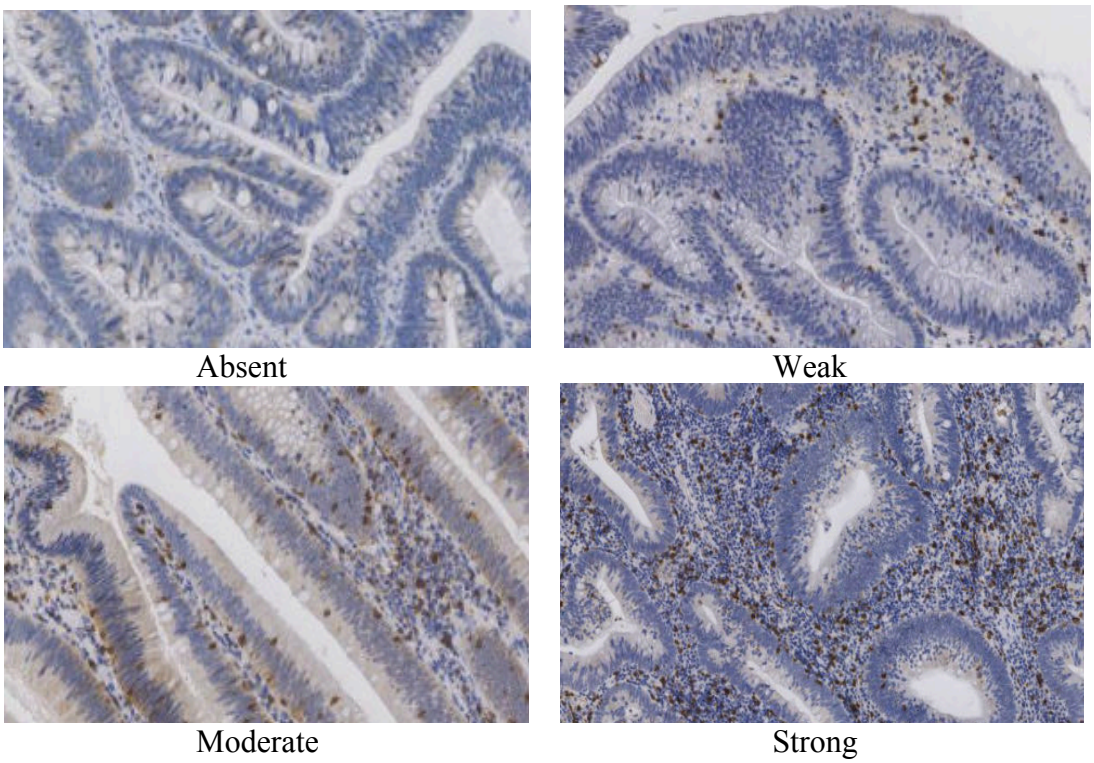
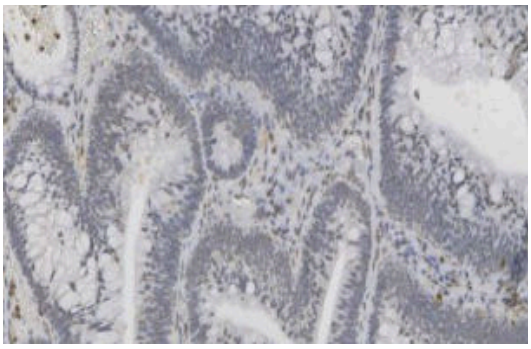
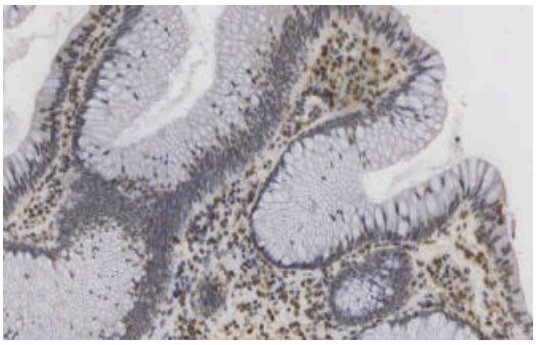


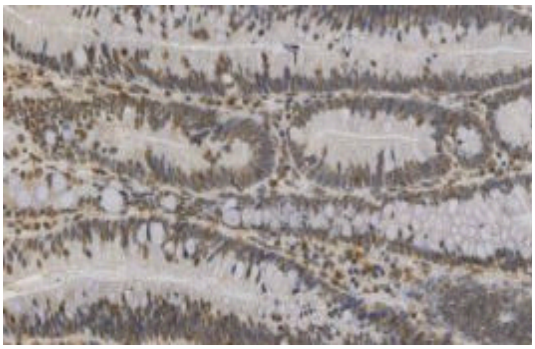
Figure 10.1b: Assessment of CD8+ cytotoxic T-lymphocyte inflammatory cell infiltrate



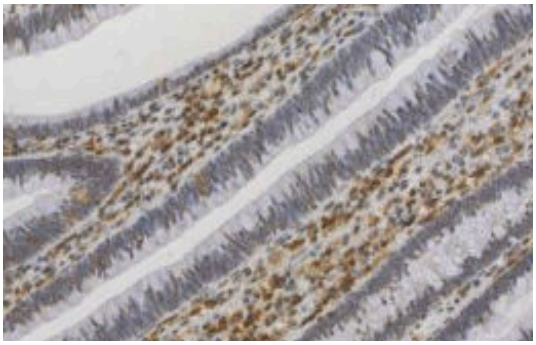
Absent



Weak

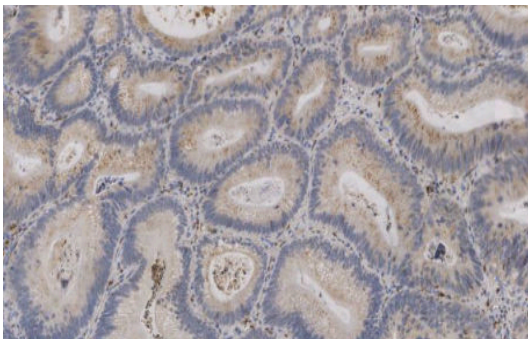


Moderate

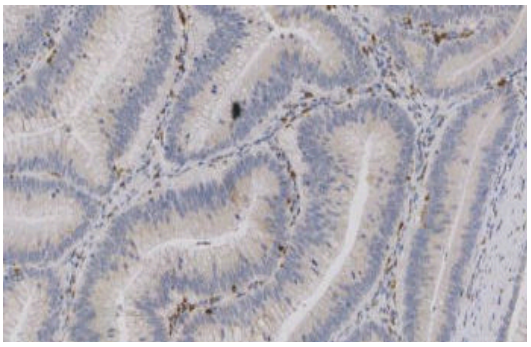


Strong

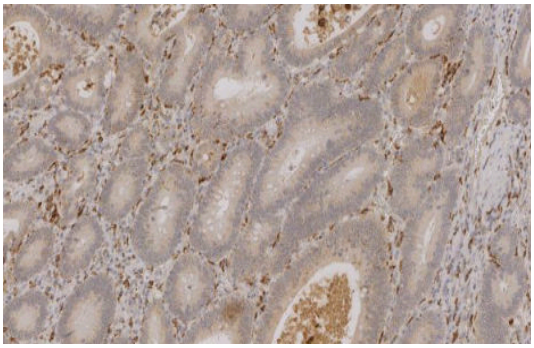
Figure 10.1c: Assessment of CD45+ helper T-lymphocyte inflammatory cell infiltrate



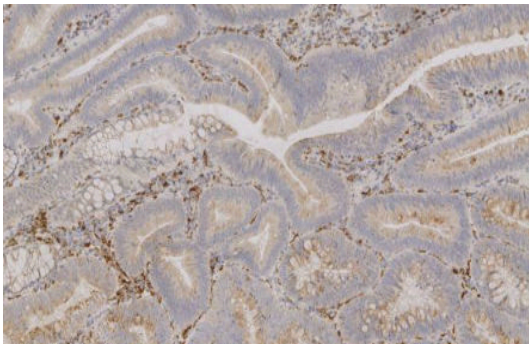
Absent



Weak



Moderate



Strong

Figure 10.1d: Assessment of CD68+ macrophage inflammatory cell infiltrate

10.4 Results

Per polyp analysis

A total of 207 polyps from 134 patients were included. 107 were high grade (HGD) and 100 were low grade (LGD). The median age of patients was 65 years and 33 (25%) were female. The majority of polyps were left sided, pedunculated and were between 10mm and 20mm in size. Only 23 (11%) of polyps had been exposed to aspirin use (Table 10.1). Comparing HGD and LGD polyps there were more older, female and less deprived patients in the HGD group (both $p<0.05$). HGD polyps were more likely to be larger and have a villous component (both $p<0.05$) (Table 10.1a). Examining the inflammatory infiltrate in polyps, high levels of CD3+, CD8+, CD45+ and CD68+ were observed in 67%, 25%, 67% and 72% of cases respectively. CD3+ infiltrate was higher in HGD polyps compared to LGD polyps (74% vs 69%, $p<0.05$). CD8+ infiltrate was higher in HGD polyps compared to LGD polyps (36% vs 13%, $p<0.001$) where as CD45+ infiltrate was similar (69% vs 64%, $p=0.401$). There was no difference in CD68+ infiltrate (74% vs 70%, $p=0.540$) (Table 10.1b) or total inflammatory cell infiltrate ($p=0.226$).

Both patient and polyp related factors were then examined to identify features associated with altered inflammatory infiltrates. There was no difference in the degree of CD3+, CD8+, CD45+ or CD68+ inflammatory infiltrate with regards to patient factors such as age, sex or deprivation. Aspirin exposure was associated with a higher level of CD45+ infiltrate ($p=0.007$). With regards to polyp factors, larger polyps were associated with a higher level of CD8+ infiltrate ($p=0.004$) and polyps with a villous component had higher levels of CD8+ infiltrate ($p=0.021$) Total inflammatory infiltrate was not related to patient or polyp factors (Table 10.2).

Per patient analysis

In order to examine whether alterations in the microenvironment were related to altered host response, a per patient paired analysis was then carried out of those patients with multiple polyps (n=46 patients) (Figure 10.2). This included those with multiple low-grade dysplastic polyps (n=24 patients) and those with multiple mixed low and high-grade dysplastic polyps (n=20 patients). Due to low numbers, analysis of the 2 patients with multiple high-grade polyps was not carried out. On paired testing using Wilcoxon signed-rank analysis there was an increase in CD3+ (p=0.059), CD68+ (p=0.046) and total inflammatory infiltrate (p=0.021) in high-grade polyps of those who had both low and high-grade dysplasia. There was no change in CD8+ (p=0.705) and CD45+ (p=0.605) infiltrate. No significant changes in inflammatory infiltrate were seen between polyps in those patients with low grade dysplasia only (CD3+, p=0.317; CD8+, p=0.083; CD45+, p=0.206; CD68+, p=0.705; total inflammatory infiltrate, p=0.617) (Figure 10.3).

Risk of recurrent / metachronous neoplasia

In those patients with a single polyp who had been included in the analysis (n=88 patients) outcome was assessed with regard to risk of recurrent or metachronous neoplasia. Of the 88 patients, 39 (44%) patients were excluded as they had multiple polyps at index colonoscopy that had not been assessed in this analysis. On follow up, with a minimum of 4 years, 34 patients had undergone at least 1 colonoscopy whereby 14 had evidence of further neoplasia (Figure 10.2).

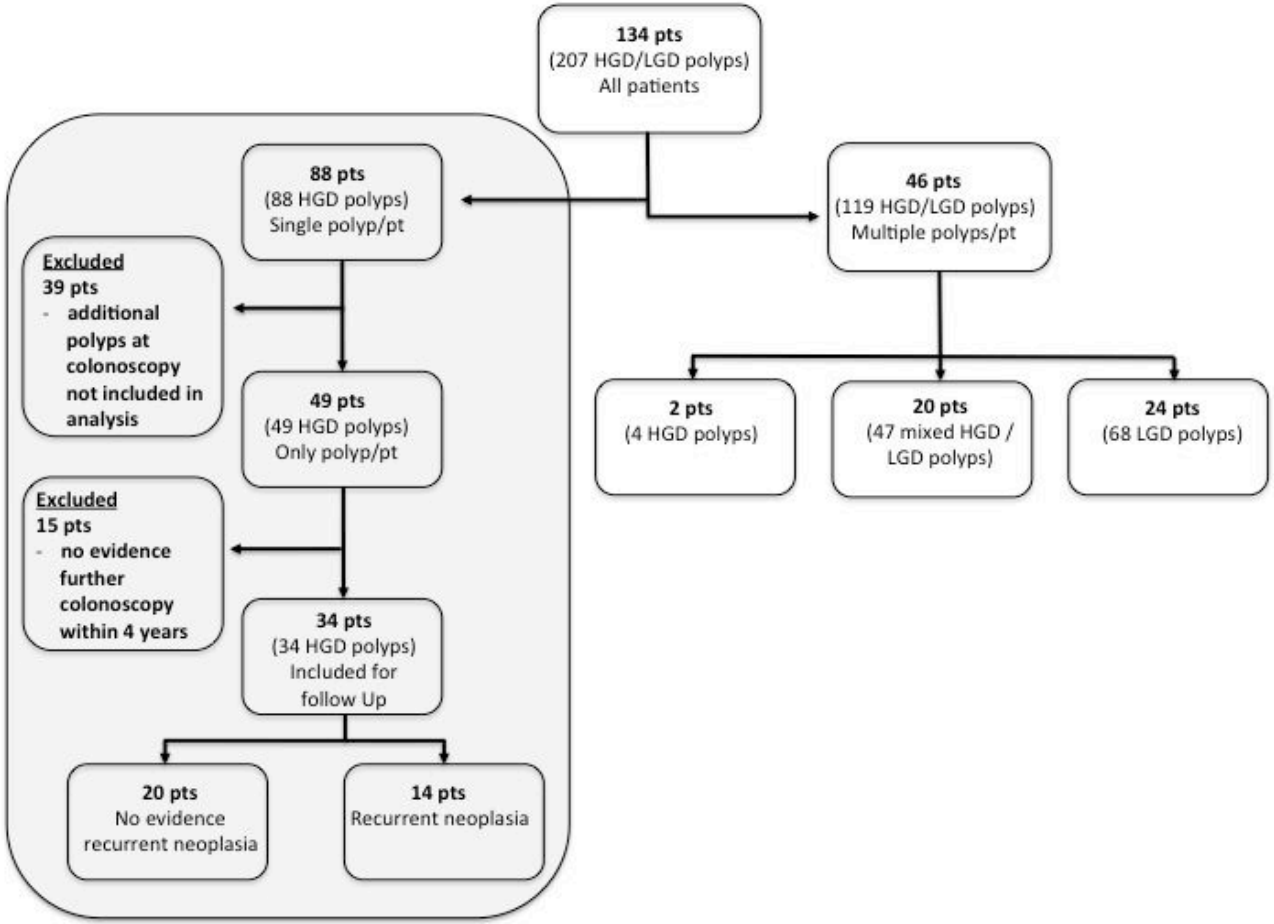
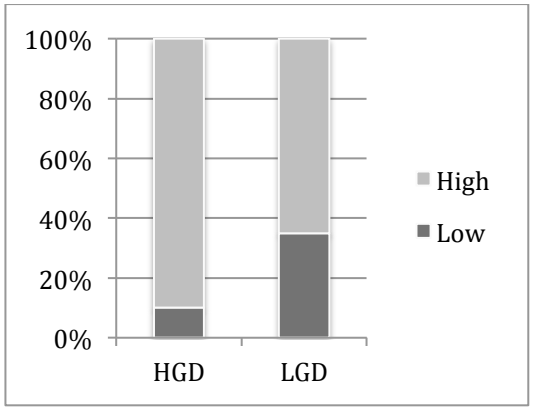
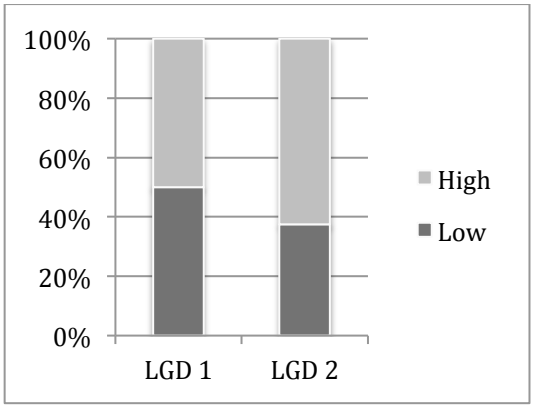


Figure 10.2: Outline of patient cohort and explanation of per patient analysis in those with multiple polyps, and follow up in those with solitary polyps (shaded box)

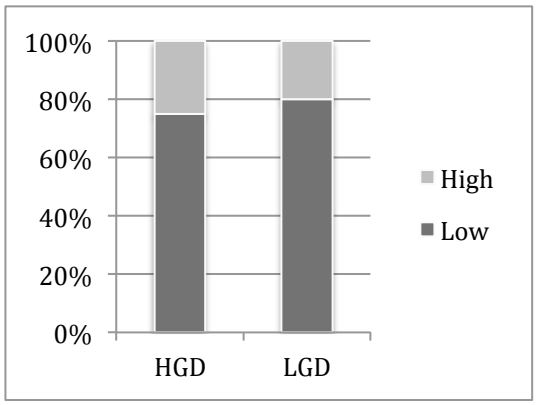
(HGD = High-grade dysplasia, LGD = Low-grade dysplasia)



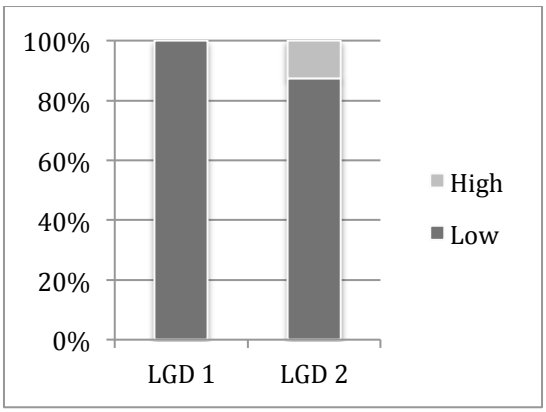
CD3+ Mixed HGD/LGD
(n=20pts, p=0.059)



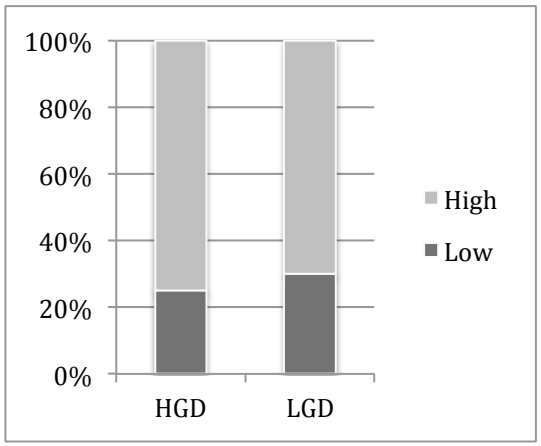
CD3+ All LGD
(n=24pts, p=0.317)



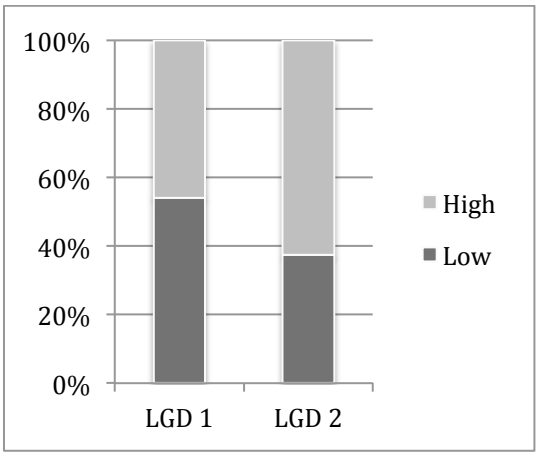
CD8+ Mixed HGD/LGD
(n=20pts, p=0.705)



CD8+ All LGD
(n=24pts, p=0.083)

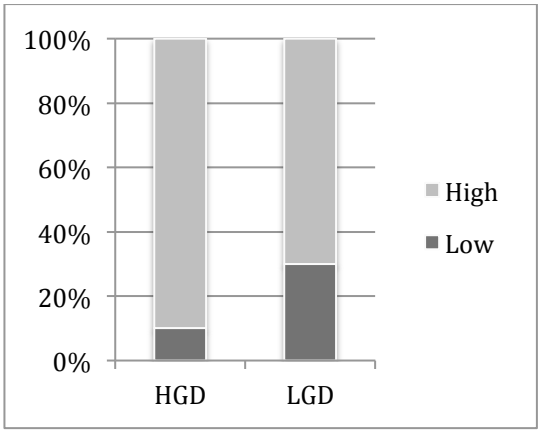


CD45+ Mixed HGD/LGD
(n=20pts, p=0.605)

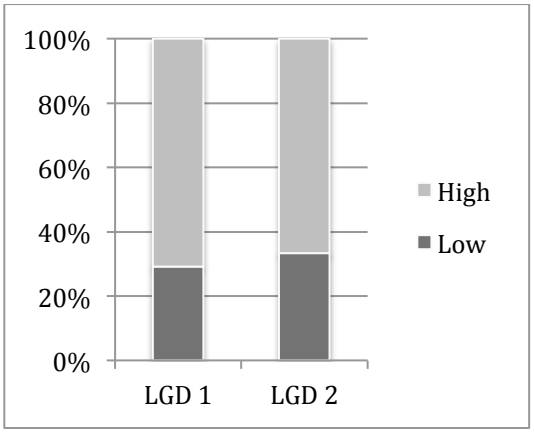


CD45+ All LGD
(n=24pts, p=0.206)

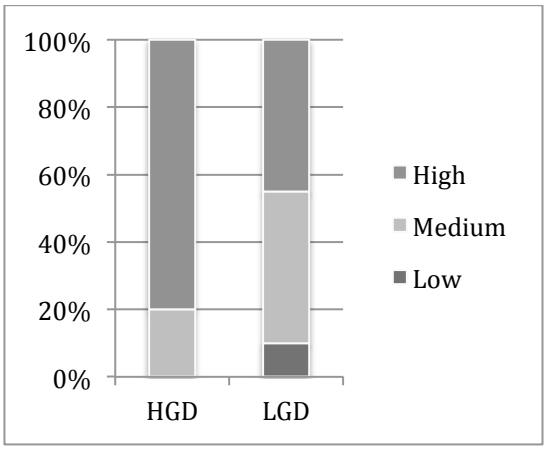
Figure 10.3a: Per patient paired analysis of CD3+, CD8+, CD45+ T-lymphocyte cell infiltrate changes between polyps in patients with multiple polyps (mixed high/low grade dysplasia or low grade dysplasia only)



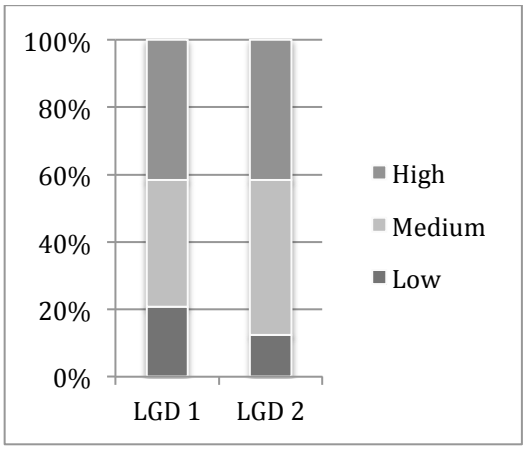
CD68+ Mixed HGD/LGD
(n=20pts, p=0.046)



CD68+ All LGD
(n=24pts, p=0.705)



Total Inflammatory Infiltrate
Mixed HGD/LGD
(n=20pts, p=0.021)



Total Inflammatory Infiltrate
All LGD
(n=24pts, p=0.617)

Figure 10.3b: Per patient paired analysis of CD68+ macrophage and total inflammatory cell infiltrate changes between polyps in patients with multiple polyps (mixed high/low grade dysplasia or low grade dysplasia only)

10.5 Discussion

The present study shows that, within the context of a colorectal cancer screening programme, there was an increase in inflammatory cell infiltrate with progression from low-grade to high-grade dysplastic polyps. This was evident whether analysed within or between patients. Therefore, it is clear that there is a specific host response to dysplastic changes in colorectal adenomas. Given the prognostic value of the tumour inflammatory cell infiltrate in established cancer (Roxburgh and McMillan 2012) it may be that the inflammatory cell infiltrate will inform the likely outcome in patients with dysplastic polyps.

The results of the present study are consistent with the observation that there is a specific interaction between adenomatous cells and the microenvironment (Cui, Yuan et al. 2009; McLean, Murray et al. 2011; Cui, Shi et al. 2012). A full understanding of the local inflammatory microenvironment of colorectal adenomas is essential if we are to learn about why some adenomas progress. The immunoediting hypothesis suggests that for neoplasia to develop there is an immune profile shift from immunosurveillance to immunosuppression (Koebel, Vermi et al. 2007). This concept suggests that the host immune response to neoplastic lesions has three phases. The first is *elimination* whereby the host immune system removes abnormal cells. The second phase is *equilibrium* where there is a development of neoplastic cells that are immune to host defences and a battle between host and tumour ensues. The final phase is *escape* whereby tumour cells overwhelm the host immunity and create a favourable microenvironment for tumour growth (Dunn, Old et al. 2004). Based on this theory, adenomatous polyps represent a neoplastic lesion in the *equilibrium* phase and hence identifying which polyps are appear more likely to *escape* would be of considerable benefit. Furthermore, modulation of this local host inflammatory microenvironment to prevent *escape* would be invaluable.

It is interesting to consider the finding of the present study with regards to patient outcome. Currently, follow-up of patients with adenomatous polyps is based on size, grade and number of polyps as previous studies have shown that patients with larger, high-grade and multiple polyps are at a higher risk of recurrence and of malignant transformation (Cairns, Scholefield et al. 2010). However, this current risk stratification technique is far from ideal and a recent population based study has suggested that there is little benefit in terms of cancer incidence reduction in following these guidelines (Loberg, Kalager et al. 2014). With just under half of all those attending for a colonoscopy following a positive bowel screening test having adenomatous polyps detected, accurate prognostic stratification is vital if we are to avoid unnecessary follow-up colonoscopy in a large proportion of the population (Logan, Patnick et al. 2012). If such a link were to be proven then it would represent a potential immunomodulatory target to help prevent the progression of adenomas in a pre-malignant phase.

The present study was predominantly cross-sectional in nature and lacked numbers to study outcome with sufficient power. However, a pilot group of 34 patients who had solitary polyps excised were followed up and a high rate of recurrent or metachronous polyps were noted (over 40% within 4 years). This should inform planning for future studies in larger numbers to explore this further and could also include those with multiple polyps. However, care should be taken with such analysis as it would be prone to potential confounding factors such as the heterogeneity of inflammatory infiltrate between polyps within the same person as has been demonstrated within the present study.

The strengths of the present study are that it is, to date, the largest study examining the local inflammatory response in colorectal adenomas. It has examined a variety of inflammatory cells using robust immunochemical techniques. In including a per patient analysis, changes in inflammatory infiltrate between different lesions within the same

colon is achieved and adds to the robustness of the findings. In addition, it has included details on aspirin usage, a potential confounder that has been missing from previous studies (Cui, Yuan et al. 2009; McLean, Murray et al. 2011). A potential additional weakness is the use of CD68+ as a marker for macrophage infiltration. When considering the immune microenvironment, macrophage subtypes associated with either an increase in the adaptive or the innate response can be of interest and CD68+ staining does not account for that. Further studies examining macrophage subtypes to explore this concept are planned in this cohort. One further potential weakness may be our use of a derived total inflammatory infiltrate rather than a true observed one. For example, in colorectal cancer the Klintrup-Makinen score, assessing inflammatory cell infiltrate at the invasive margin on routinely stained H&E slides, has been widely validated as means of observing a total inflammatory cell infiltrate and has been correlated with patient outcome (Klintrup, Makinen et al. 2005). However, as discussed in Chapter 9, the nature of endoscopic polyp resections, where there is no clear margin in the majority of cases, means that inflammatory cell infiltrate can only be examined within the adenoma itself and not at the margin. Therefore the Klintrup-Makinen score cannot accurately be assessed.

In conclusion, the present chapter has shown an increase in inflammatory infiltrate with progression from low-grade to high-grade dysplasia. This would suggest a specific response to early disease progression confirming increased host immunosurveillance. Therefore, it may be possible that such a finding may have a use in the prognostic stratification and treatment of dysplastic polyps.

Table 10.1a: Baseline characteristics of adenomatous polyps by grade of dysplasia (per polyp analysis)

	All polyps	Low-grade polyps	High-grade polyps	p-value
	n(%)	n(%)	n(%)	
	207	100	107	
Age				
<65	111 (54)	61 (61)	50 (47)	
≥65	96 (46)	39 (39)	57 (53)	0.040
Sex				
Male	166 (80)	88 (88)	78 (73)	
Female	41 (20)	12 (12)	29 (27)	0.006
Deprivation Quintile				
1 (most deprived)	81 (40)	49 (51)	32 (30)	
2	25 (12)	8 (8)	17 (16)	
3	36 (18)	21 (21)	15 (14)	
4	23 (11)	6 (6)	17 (16)	
5 (least deprived)	39 (19)	13 (13)	26 (24)	0.003
Aspirin exposure				
Yes	23 (11)	9 (9)	14 (13)	
No	182 (89)	89 (91)	93 (87)	0.377
Adenoma location				
Proximal to splenic flexure	27 (13)	16 (16)	11 (10)	
Distal to splenic flexure	180 (87)	84 (84)	96 (90)	0.223
Macroscopic appearance				
Sessile	53 (26)	28 (28)	25 (23)	
Pedunculated	154 (74)	72 (72)	82 (77)	0.445
Size (mm)				
10-12	48 (23)	32 (32)	16 (15)	
13-15	54 (54)	25 (25)	29 (27)	
16-20	59 (59)	28 (28)	31 (29)	
>20	46 (22)	15 (15)	31 (29)	0.002
Microscopic appearance				
Tubular	88 (43)	50 (50)	38 (36)	
Tubulovillous/villous	119 (57)	50 (50)	69 (64)	0.036

Table 10.1b: Comparison of inflammatory infiltrate by grade of adenomatous polyp (per polyp analysis)

	All polyps	Low-grade polyps	High-grade polyps	p-value
	n(%)	n(%)	n(%)	
	207	100	107	
CD3+				
High	140 (67)	61 (61)	79 (74)	
Low	67 (32)	39 (39)	28 (26)	0.049
CD8+				
High	52 (25)	13 (13)	39 (36)	
Low	155 (75)	87 (87)	68 (64)	<0.001
CD45+				
High	137 (67)	63 (64)	74 (69)	
Low	69 (33)	36 (36)	33 (31)	0.401
CD68+				
High	149 (72)	70 (70)	79 (74)	
Low	58 (28)	30 (30)	28 (26)	0.540
Total inflammatory infiltrate				
Low	30 (15)	17 (17)	13 (12)	
Med	65 (31)	35 (35)	30 (28)	
High	112 (54)	48 (48)	64 (60)	0.226

Table 10.2: Associations between adenomatous polyp and host variables and degree of inflammatory infiltrate (per polyp analysis)

	T-lymphocytes CD3+ *(p-value)*	**Cytotoxic T-cells CD8+** *(p-value)*	**Helper T-cells CD45+** *(p-value)*	**Macrophages CD68+** *(p-value)*	**Total inflammatory infiltrate** (*p-value)*
Age (<65 / ≥65)	0.566	0.970	0.152	0.732	0.665
Sex (Male / Female)	0.397	0.059	0.168	0.850	0.800
Deprivation Quintile (1/2/3/4/5)	0.252	0.416	0.866	0.128	0.470
Aspirin exposure (Yes / No)	0.235	0.887	**0.007**	0.888	0.533
Polyp location (Proximal / Distal to splenic flexure)	0.443	0.291	0.648	0.842	0.863
Macroscopic appearance (Sessile / Pedunculated)	0.283	0.396	0.630	0.312	0.451
Size (<20mm / ≥20mm)	0.081	**0.004**	0.058	0.410	0.529
Microscopic appearance (Tubular / Tubulovillous/villous)	0.877	**0.021**	0.293	0.604	0.675
Grade of polyp (Low / High)	**0.049**	**<0.001**	0.401	0.540	0.226

11 CONCLUSIONS

11.1 Overview of thesis

Screening for colorectal cancer has been introduced to reduce cancer specific mortality through the detection of early stage disease. However, at the beginning of this period of research it was apparent that population based screening programmes were still in their infancy and it remained unclear what the true impact would be. Moreover, geographical differences, particularly in terms of the demographic profile of the population invited to screening, were vitally important to its efficacy. Therefore, application of trial results to our socioeconomically deprived population may not be valid. Furthermore it was apparent that outside of TNM Stage, there had been little work exploring differences between screen-detected and non screen-detected disease. There is a wealth of evidence that additional tumour and host prognostic factors are of importance in determining outcome however, these have yet to be examined in the screen-detected population. In particular, the systemic inflammatory response has been consistently shown to be indicative of those patients who have a worse outcome, however has not been explored within screen-detected or early stage disease.

Chapter 2 began by putting the current bowel screening programme into context by providing an overview into the site, stage and mode of presentation of colorectal cancer within our geographical area of study. By utilising population based data it could be shown that accompanying the introduction of screening, a rise in early stage disease has been seen. By examining pre, during and post screening introduction cohorts the timing of the change was explored and seen to mirror screening introduction. However, it became apparent that there were some limitations of using such large datasets. It was able to provide an overview of presentation within the region however lacked sufficient detail to explore detailed tumour and host variables.

Therefore, Chapter 3 sought to examine the first round of the screening programme in more detail to explore outcome through all stages of the screening programme. Data was initially extracted from the local Bowel Screening IT System and then on a case-by-case basis all those attending for colonoscopy were examined in more detail. Such labour intensive data collection was deemed necessary to ensure accuracy that was not possible with the population dataset used for Chapter 2. It highlighted the importance of deprivation in impacting outcome at all stages of the screening pathway. For example, it was discovered that deprivation was associated with not only uptake of the test, but the risk of a positive test, the likelihood of undergoing colonoscopy following a positive test and also the risk of having cancer detected at colonoscopy following a positive test.

The rational behind Chapter 4 was that one of the criticisms of gFOBt based population screening is that a disproportionate number of left sided tumours are identified. This is thought to arise due to degradation of haemoglobin through gut transit rendering it less sensitive for right-sided lesions. This was indeed noted in our population and identified in Chapter 3. Therefore, it was theorised that use of a flexible sigmoidoscopy-first approach may be adequate to examine the large bowel in these patients. Such a change to the screening algorithm would have significant cost and resource implications. However, the results of this chapter show that a significant number of right sided lesions would be missed and it was concluded that such a change in the process would neither be feasible nor desirable.

Through examination of the first round of screening in detail (Chapter 3) it became apparent that the colonoscopy dataset generated could be used to observe other factors associated with colorectal cancer risk. This led to an exploration of the potential chemopreventative effects of commonly used cardiovascular drugs such as aspirin, statins and ACE-inhibitors (Chapter 5) and also of the value of symptoms in predicting cancer risk

(Chapter 6). Chapter 5 reported that individuals on these commonly used medications either in isolation or combination, were less likely to have cancer, significant neoplasia or neoplasia than those who were not. This supports evidence from observational studies that have shown this outside of a screening cohort and supports the concept that these are potentially chemopreventative medications. Chapter 6 utilised data on symptoms collected at pre-assessment and correlated this with outcome at colonoscopy. One of the major driving factors behind the development of national screening programmes is previous research showing poor relationship between bowel symptoms and detection of colorectal cancer at colonoscopy. There was a high rate of common lower GI symptoms (around 40% of all patients undergoing colonoscopy following a positive screening test) and this actually negatively correlated with risk of cancer or neoplasia. This suggests that within the context of a national screening programme, recording of symptoms is of limited value.

Through data linkage with the Managed Clinical Network dataset it was possible to identify those invited to screening whom subsequently had colorectal cancer detected outwith the screening programme (Chapter 7). This included those who had not responded to the invitation and those who had tested negative. This allowed an estimation of the sensitivity and specificity of the first round of screening in our geographical area. In addition it allowed for direct comparison of tumour and host prognostic factors between screen-detected and non screen-detected disease. This is the first time the host systemic response has been examined within the context of a national bowel screening programme. Screen-detected tumours were of an earlier stage than those detected outwith screening and, within TNM Stage II and TNM Stage III disease, had more favourable tumour and host prognostic factors.

One of the limitations of examining the screen-detected cohort is that there is limited follow-up of this immature cohort. However, as identified in Chapter 7, there appears to be

little difference between screen-detected and non screen-detected colorectal cancer at an early stage and therefore findings on mature follow-up of non-screen detected TNM Stage I disease should be applicable to the screened cohort. Hence, Chapter 8 utilised a separate cohort from prior to the advent of screening in our geographical area to explore outcomes specifically in TNM Stage 1 disease. There is a lack of evidence regarding outcomes in early stage disease as it is something that has not been seen previously in large numbers. As has been shown in Chapter in 2 it is likely to be increasingly relevant in the post-screening era where it may account for approximately a third of all non-metastatic colorectal cancer. It was found that cancer specific survival was excellent (95% at 5 years), however overall survival was less good (76% at 5 years) and that the presence of a elevated pre-operative systemic inflammatory response could predict those with a worse overall outcome.

The final analysis of the thesis involved tissue work exploring the role of the local inflammatory response within screen-detected early stage colorectal cancer (Chapter 9) and premalignant adenomatous polyps (Chapter 10). When examining T1/2 disease there was evidence of higher levels of lymphatic involvement (including nodal disease) in T2 tumours compared to T1 disease, however rates of venous invasion and the local peri-tumoural inflammatory response were unchanged. This suggested that venous invasion and the local response occurred early in the disease process. There was difficulty in including patients for analysis due to high levels of patients with T1/2 disease undergoing endoscopic resection and hence not having an invasive margin on which the peri-tumoural inflammatory response could be assessed. Therefore, the decision was made to use immunohistochemistry to assess the intra-tumoural infiltrate in pre-malignant adenomatous polyps (Chapter 10). There was evidence of a more pronounced inflammatory infiltrate between low and high-grade dysplastic polyps which was noted both overall in the cohort, and also in a paired analysis of patients who had both low and high-grade dysplastic

polyps. This suggests a specific response to early disease progression confirming increased host immunosurveillance. Therefore, it may be possible that such a finding may have a use in the prognostic stratification and treatment of dysplastic polyps.

11.2 Future work

This thesis is the exploration of individuals invited to the prevalence round of screening in our geographical area. As such, it represents an immature cohort in whom outcome or survival analysis has not been possible. Clearly, future work exploring survival between individuals with screen-detected and non screen-detected colorectal cancer is required to assess what impact the differing tumour and host prognostic factors play in determining outcome. In particular, this thesis has demonstrated that patients with screen-detected TNM Stage II and III disease have a different host preoperative systemic inflammatory response. It has yet to be shown that this will retain its significance as a prognostic factor within screen-detected disease and future studies examining this are planned in this cohort.

It is important to consider that population FOBt screening is a dynamic process, designed to be repeated in order to ensure efficacy, and so further work examining how these differences alter over subsequent rounds is also planned. In particular, as subsequent incidence rounds of screening continue, it is unclear what effect this will have on stage of presentation at a population level. Furthermore, the SBoSP is in the development phase of a change in the existing screening algorithm to utilise quantitative FIT rather than gFOBt as a first line test. This is due to commence in 2017, and is expected to affect not only positivity rates, but also participation, as it has been shown to be an easier test to perform. It will be of interest over the forthcoming years to examine screening uptake and efficacy as these changes are implemented in our deprived population.

Overall, it is likely that the shift towards early stage disease identified in this thesis will continue and will be aided not only through improvements in the screening algorithm but also population campaigns such as Detect Cancer Early. It is likely therefore that there will be an increased focus on outcomes in TNM Stage I disease as larger numbers of these are detected. While overall cancer-specific outcome is excellent, identifying which individuals

require more intensive follow-up and who can be reassured is important not only from a patient perspective but also from a societal perspective in terms of resource utilisation. This is particularly pertinent with screen-detected early stage disease where one of the risks is of medicalisation of an otherwise healthy individual. Furthermore, examining T1/2 disease allows us to enhance our understanding of early tumour growth and provides potential opportunities for early intervention. It has been demonstrated in this thesis that the preoperative systemic inflammatory response identifies a subset of patients who have a poorer overall survival following resection of TNM Stage I disease. A cancer diagnosis has been identified as a teachable moment where individuals are more susceptible to a positive health intervention. Therefore, it would seem practical to propose that patients with an elevated preoperative systemic inflammatory response are a subset that should be targeted. This could include both lifestyle and pharmacological interventions, aimed at reducing systemic inflammation, which may ultimately improve outcomes. Further studies, could include the instigation of such a rehabilitation programme in a manner not dissimilar to cardiac rehabilitation which is now a standard of care for patients who have undergone a cardiac event.

Examining the tumour-host interface at a local level, this thesis has characterised the peri-tumoural inflammatory infiltrate in screen-detected T1/2 disease. It has validated the previously created automated method of assessing this in early stage disease. One problem with this analysis was that a large proportion of patients with T1/2 disease were managed endoscopically and were hence excluded from this analysis. There are currently no validated means of assessing the local inflammatory infiltrate in polypectomy specimens. Further work identifying such a method should be developed to allow full characterisation of the local inflammatory response in early stage disease. Moreover, any studies on outcomes in early stage disease, including malignant polyps, require large numbers with long-term follow-up. Data on screen-detected malignant polyps identified during the

course of this thesis has been included in the Scottish Screen-detected Polyp Cancer Study (SSPoCS) which is due to publish outcomes within the next year. This is a national study of all screen-detected malignant polyps since the advent of screening in Scotland. Future studies examining what role the local inflammatory response has in malignant polyps should be undertaken and could utilise such a resource.

Finally, screening has the potential to amass considerable population datasets that allow us to explore the natural history of colorectal cancer from its earliest stages of development. It would seem prudent to assume that if outcome following resection for colorectal cancer depends on the interaction between tumour and host, as witnessed by both the systemic inflammatory response and the local inflammatory response at the invasive margin, then the risk of transformation from premalignant adenomatous polyp to invasive carcinoma should do so too. Such a finding would have the potential to fundamentally alter our concept of risk-stratification in individuals with adenomatous polyps and may also identify a potential immunomodulatory therapeutic target. This should be the focus of further prospective observational studies and utilising screen-detected individuals would seem the most effective way of doing this.

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